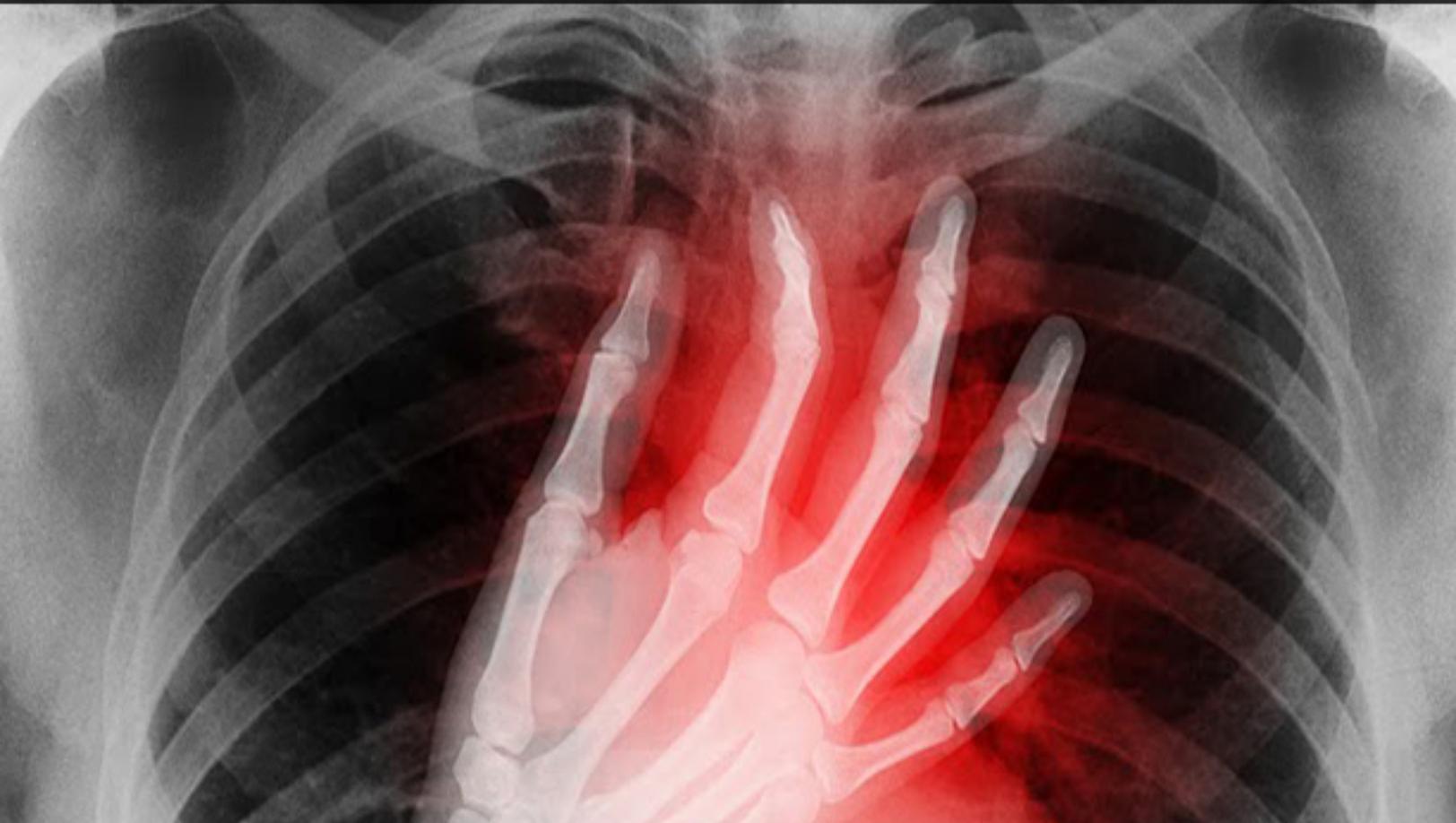


# Pulmonology and Respiratory Diseases



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First Edition, 2012

ISBN 978-81-323-1430-1

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*Published by:*

**College Publishing House**  
4735/22 Prakashdeep Bldg,  
Ansari Road, Darya Ganj,  
Delhi - 110002  
Email: [info@wtbooks.com](mailto:info@wtbooks.com)

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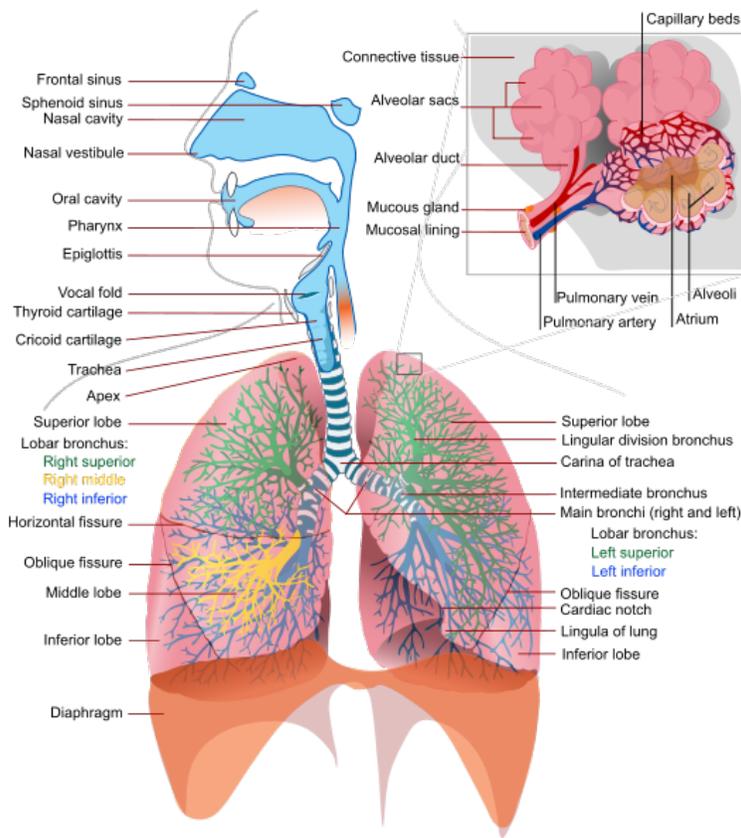
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# Chapter 1

# Pulmonology

## Pulmonologist



A complete view of the respiratory system.

### Occupation

**Names** Doctor, Medical Specialist

**Type** Specialty

**Activity sectors** Medicine

### Description

**Education required** Doctor of Medicine

## Fields of employment

Hospitals, Clinics

In medicine, **pulmonology** (aka **pneumology**) is the specialty that deals with diseases of the respiratory tract and respiratory disease. It is called **chest medicine** and **respiratory medicine** in some countries and areas. *Pulmonology* is generally considered a branch of internal medicine, although it is closely related to intensive care medicine (aka critical care medicine) when dealing with patients requiring mechanical ventilation. **Chest medicine** is not a specialty in itself but is an inclusive term which pertains to the treatment of diseases of the chest and contains the fields of pulmonology, thoracic surgery, and intensive care medicine. Pulmonology is concerned with the diagnosis and treatment of lung diseases, as well as secondary prevention (tuberculosis). Physicians specializing in this area are called pulmonologists. In the United Kingdom, Ireland, South Africa and Australia the term "respiratory physician" is used rather than pulmonologist. In Canada, respirology and respirologist are used. Surgery of the respiratory tract is generally performed by specialists in cardiothoracic surgery (or thoracic surgery), though minor procedures may be performed by pulmonologists. As mentioned above, pulmonology is closely related to critical care medicine when dealing with patients that require mechanical ventilation. As a result, many pulmonologists are certified to practice critical care medicine in addition to pulmonary medicine. There are fellowship programs that allow physicians to become board certified in pulmonary and critical care medicine simultaneously. Interventional pulmonology is a relatively new field within pulmonary medicine that deals with the use of procedures such as bronchoscopy to treat several pulmonary diseases. Interventional pulmonology is not its own specialty.

## ***History of pulmonology***

One of the first major discoveries pertaining to pulmonology was the discovery of pulmonary circulation. Originally, it was thought that blood reaching the right side of the heart passed through small 'pores' the septum into the left side to be oxygenated, as theorized by Galen; however, the discovery of pulmonary circulation disproves this theory, which had previously been accepted since the second century. Thirteenth century anatomist and physiologist Ibn Al-Nafis accurately theorized that there was no 'direct' passage between the two sides (ventricles) of the heart. He believed that the blood must have passed through the pulmonary artery, through the lungs, and back into the heart to be pumped around the body. This is believed by many to be the first scientific description of pulmonary circulation.

Although pulmonary medicine only began to evolve as a medical specialty in the 1950's, William Welch and William Osler founded the 'parent' organization of the American Thoracic Society, the National Association for the Study and Prevention of Tuberculosis. When the specialty did begin to evolve, several discoveries were being made linking the respiratory system and the measurement of arterial blood gases, attracting more and more physicians and researchers to the developing field.

## ***Diagnosis***

The pulmonologist begins the diagnostic process with a general review focusing on:

- hereditary diseases affecting the lungs (cystic fibrosis, alpha 1-antitrypsin deficiency)
- exposure to toxins (tobacco smoke, asbestos, exhaust fumes, coal mining fumes)
- exposure to infectious agents (certain types of birds, malt processing)
- an autoimmune diathesis that might predispose to certain conditions (pulmonary fibrosis, pulmonary hypertension)

Physical diagnostics are as important as in the other fields of medicine.

- Inspection of the hands for signs of cyanosis or clubbing, chest wall, and respiratory rate.
- Palpation of the cervical lymph nodes, trachea and chest wall movement.
- Percussion of the lung fields for dullness or hyperresonance.
- Auscultation (with a stethoscope) of the lung fields for diminished or unusual breath sounds.
  - Rales or Rhonchi heard over lung fields with a stethoscope.

As many heart diseases can give pulmonary signs, a thorough cardiac investigation is usually included.

Other tools include:

- Laboratory investigation of blood (blood tests). Sometimes arterial blood gas measurements are also required.
- Spirometry (the determination of lung volumes in time by breathing into a dedicated machine; response to bronchodilators and diffusion of carbon monoxide)
- Bronchoscopy with bronchoalveolar lavage (BAL), endobronchial and transbronchial biopsy and epithelial brushing
- Chest X-rays
- CT scanning (MRI scanning is rarely used)
- Scintigraphy and other methods of nuclear medicine
- Positron emission tomography (especially in lung cancer)
- Polysomnography (sleep studies) commonly used for the diagnosis of Sleep apnea

## ***Treatment***

Surgical treatment is generally performed by the (cardio)thoracic surgeon, generally after primary evaluation by a pulmonologist. Medication is the most important treatment of most diseases of pulmonology, either by inhalation (bronchodilators and steroids) or in oral form (antibiotics, leukotriene antagonists). A common example being the usage of inhalers in the treatment of inflammatory lung conditions such as Asthma or Chronic

obstructive pulmonary disease. Oxygen therapy is often necessary in severe respiratory disease (emphysema and pulmonary fibrosis). When this is insufficient, the patient might require mechanical ventilation.

Pulmonary rehabilitation or respiratory therapy may be initiated as a treatment after all or most other treatments do little to help the patient. Pulmonary rehabilitation is for patients whose respiratory function has decreased or improved very little, even with extensive medical treatment. Pulmonary rehabilitation is intended to educate the patient, the family, and improve the overall quality of life and prognosis for the patient. Although a pulmonologist may refer a patient to therapy, the therapy is generally practiced by respiratory therapists.

### ***Pulmonology as a career***

In the United States, pulmonologists are physicians who, after receiving a medical degree (MD or DO), complete residency training in internal medicine (3 years), followed by at least 2 additional years of subspecialty fellowship training in pulmonology. After satisfactorily completing a fellowship in pulmonary medicine, he or she is permitted to take the board certification examination in pulmonary medicine. After passing this exam, he or she is now board certified. Most pulmonologists complete 3 years of combined subspecialty fellowship training in pulmonary medicine and critical care medicine.

In the United States, pediatric pulmonologists are physicians who, after receiving a medical degree (MD or DO), complete residency training in pediatrics (3 years), followed by at least 3 additional years of subspecialty fellowship training in pulmonology.

Usually, respiratory problems can be managed by a specialist in internal medicine; however, some cases require the attention of a pulmonologist. Usually, a pulmonologist will be required in advanced cases of many respiratory diseases.

### ***Scientific research***

Pulmonologists are involved in both clinical and basic research of the respiratory system, ranging from the anatomy of the respiratory epithelium to the most effective treatment of pulmonary hypertension (a disease notoriously resistant to therapy). Scientific research also takes place to look for causes and possible treatment in diseases such as pulmonary tuberculosis and lung cancer. Several societies are dedicated to expanding the field of pulmonary medicine, some of which are listed below:

- American College of Chest Physicians
- American Lung Association
- American Thoracic Society
- British Thoracic Society
- European Respiratory Society

## Chapter 2

# Acute Exacerbations of Chronic Bronchitis

**Acute exacerbations of chronic bronchitis (AECB)** are episodes of difficulty in breathing in a person with chronic bronchitis.

In concomitant presence of emphysema, the underlying condition can be classified as chronic obstructive pulmonary disease (COPD), and the exacerbations termed "acute exacerbation of COPD", and shares many characteristics with that of AECB.

### ***Incidence***

The incidence of AECB varies depending on which definition is used, but by AECB definitions by *Anthonisen et al.* the typical COPD patient averages two to three AECB episodes per year. With a COPD prevalence of more than 12 million (possibly 24 million including undiagnosed ones) in the United States, there are at least 30 million incidences of AECB annually in the US.

### ***Pathogenesis***

During AECB, breathing becomes much more difficult because of further narrowing of the airways, in addition to increased secretion of mucus, which often is thicker than usual.

### ***Causes***

AECB can be caused by:

- Allergens, e.g., pollens, wood or cigarette smoke, pollution
- Toxins, including a variety of different chemicals
- Acute viral or bacterial infections. The extra mucus in the airways in chronic bronchitis provides a good place for viruses and bacteria to grow. Bacterial infections are suspected when there is a yellow or greenish colour of the mucus, or it is thicker than usual. However, coloured mucus is not specific to bacterial infections. Common bacterial pathogens of acute exacerbations include *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*.

Less common bacterial pathogens include *Chlamydia pneumoniae* and *MRSA*. Pathogens seen more frequently in patients with impaired lung function (FEV<sub>1</sub><35% of predicted) include *Haemophilus parainfluenzae* (after repeated use of antibiotics), *Mycoplasma pneumoniae* and gram-negative, opportunistic pathogens like *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

Although the condition of a patient with chronic bronchitis can become exacerbated by many other factors as well, the scope is generally restricted to the ones that cause the symptoms below.

## **Symptoms**

An acute exacerbation of chronic bronchitis is associated with increased frequency and severity of coughing. It is often accompanied by worsened chest congestion and discomfort. Shortness of breath and wheezing are present in many cases.

In infection, there is often weakness, fever and chills. If due to a bacterial infection, the sputum may be slightly streaked with blood and coloured yellow or green.

## **Diagnosis**

The diagnostic criteria for acute exacerbation of chronic bronchitis generally include an production of sputum that is purulent and may be thicker than usual, but without evidence of pneumonia (which involves mainly the alveoli rather than the bronchi). Also, diagnostic criteria may include an increased in frequency and severity of cough, as well as increased shortness of breath.

A chest X-ray is usually performed on people with fever and, especially, hemoptysis (blood in the sputum), to rule out pneumonia and get information on the severity of the exacerbation. Hemoptysis may also indicate other, potentially fatal, medical conditions.

A history of exposure to potential causes and evaluation of symptoms may help in revealing the cause of an acute exacerbation of chronic bronchitis, which helps in choosing the best treatment. A sputum culture can specify which strain is causing a bacterial AECB. An early morning sample is preferred.

## **Prevention**

Prevention of AECB include:

- Smoking cessation and avoiding dust, passive smoking, and other inhaled irritants
- Yearly influenza and pneumococcal vaccine
- Regular exercise, appropriate rest, and healthy nutrition
- Avoiding people currently infected with e.g. cold and influenza
- Maintaining good fluid intake and humidifying the home, in order to help reduce the formation of thick sputum and chest congestion.

## Treatment

Treatment is often started before the test results confirm the condition.

Treatment of AECB may include:

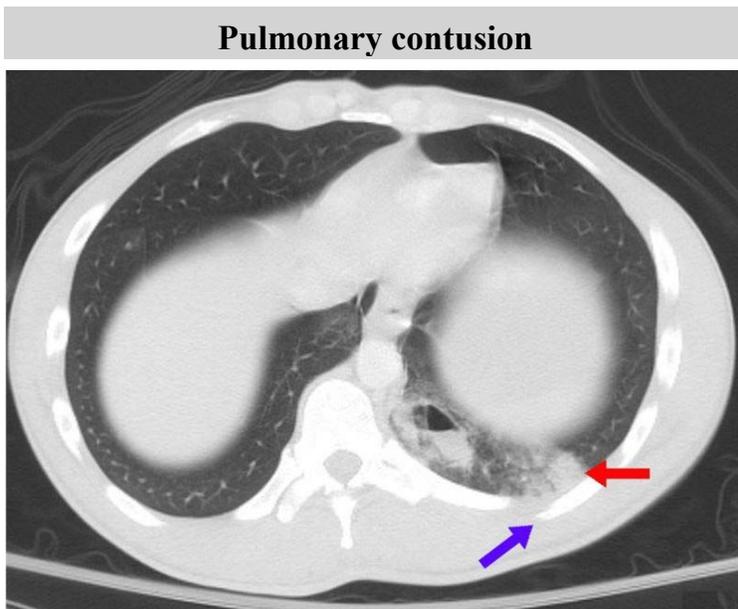
- Mucolytic agents may be used to help liquefy thick mucus, facilitating clearance from the airways. Thinning of mucus may also be done by drinking plenty of fluids.
- Inhaled bronchodilators open up the airways in the lungs. These include salbutamol and terbutaline (both  $\beta_2$ -adrenergic agonists), and ipratropium (an anticholinergic).
- Antibiotics are used if a bacterial infection is the suspected cause. However, antibiotics will not treat exacerbations caused by viruses. Viral infections will usually be cured with time with the aid of proper rest and care. Still, other medications may be needed to control symptoms. Lipid-soluble antibiotics such as macrolides, tetracyclines, and quinolones penetrate the lung tissue well. Macrolides are more active against *Streptococcus pneumoniae* than the tetracyclines and the older quinolones. Within the macrolides, newer ones are more active against *Haemophilus influenzae* than the older erythromycin. Regimens should generally be given for five days. Choice of antibiotics is also dependent on the severity of chronic bronchitis:
  - "Simple" chronic bronchitis is generally where the patient is 65 years or less, has fewer than four exacerbations per year, has minimal or moderate impairment in respiratory function and no comorbid disease. In patients with "simple" chronic bronchitis, therapy should be targeted towards *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and possibly pathogens of atypical pneumonia. The first-line treatment is a beta-lactam antibiotic such as amoxicillin. The choice will depend on resistance patterns. In patients with penicillin allergy, doxycycline or trimethoprim are preferred.
  - More complicated bronchitis may be when the patient is more than 65 years old, has four or more exacerbations per year, has an FEV1/FVC ratio of less than 50% on spirometry, has failed to respond to previous antibiotic treatment, and/or has comorbidity. In these cases, treatment should be aimed at Gram-negative bacteria and the possibility of high antibiotic resistance should be considered. Sputum culture results are of great value in determining antibiotic resistance. First-line treatment is cefuroxime or co-amoxiclav. Third-line treatment, as well as treatment in penicillin-allergic patients, is a fluoroquinolone such as ciprofloxacin. An agent active against *Streptococcus pneumoniae* may have to be added.
- Corticosteroids such as prednisone reduce inflammation in the airways. They are usually used for short periods.
- Theophylline, taken orally, helps to ease the difficulty of breathing. It may be added if the patient is not already taking it for the chronic bronchitis.

- Oxygen therapy should be initiated if there is a substantial risk of hypoxia. If oxygen is required on an ongoing basis, a portable oxygen concentrator can be used.

There should also be a "care plan" in case of future exacerbations. Patients may watch for symptoms, such as shortness of breath, change in character or amount of mucus, and start self-treatment as discussed with a health care provider. This allows for treatment right away until a doctor can be seen.

## Chapter 3

# Pulmonary Contusion



A CT scan showing a pulmonary contusion (red arrow) accompanied by a rib fracture (blue arrow)

**ICD-10**            S27.3

**ICD-9**            861.21, 861.31

A **pulmonary contusion** (or **lung contusion**) is a contusion (bruise) of the lung, caused by chest trauma. As a result of damage to capillaries, blood and other fluids accumulate in the lung tissue. The excess fluid interferes with gas exchange, potentially leading to inadequate oxygen levels (hypoxia). Unlike pulmonary laceration, another type of lung injury, pulmonary contusion does not involve a cut or tear of the lung tissue.

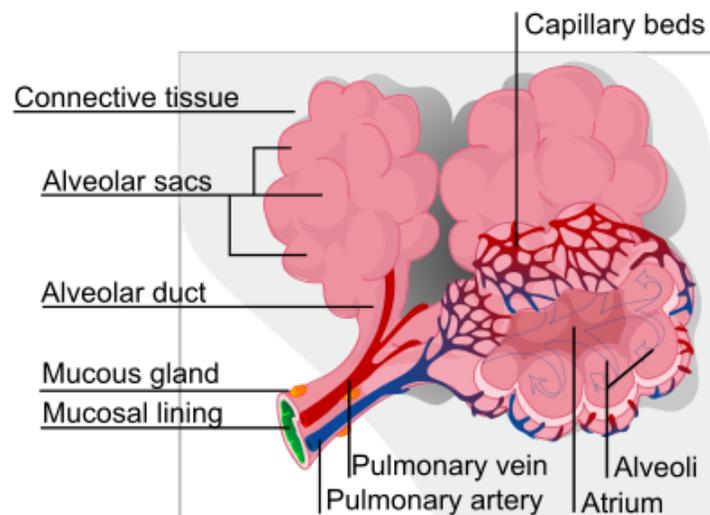
A pulmonary contusion is usually caused directly by blunt trauma but can also result from explosion injuries or a shock wave associated with penetrating trauma. With the use of explosives during World Wars I and II, pulmonary contusion resulting from blasts gained recognition. In the 1960s its occurrence in civilians began to receive wider

recognition, in which cases it is usually caused by traffic accidents. The use of seat belts and airbags reduces the risk to vehicle occupants.

Diagnosis is made by studying the cause of the injury, physical examination and chest radiography. Typical signs and symptoms include direct effects of the physical trauma, such as chest pain and coughing up blood, as well as signs that the body is not receiving enough oxygen, such as cyanosis. The contusion frequently heals on its own with supportive care. Often nothing more than supplemental oxygen and close monitoring is needed; however, intensive care may be required. For example, if breathing is severely compromised, mechanical ventilation may be necessary. Fluid replacement may be required to ensure adequate blood volume, but fluids are given carefully since fluid overload can worsen pulmonary edema, which may be lethal.

The severity ranges from mild to deadly—small contusions may have little or no impact on the patient's health—yet pulmonary contusion is the most common type of potentially lethal chest trauma. It occurs in 30–75% of severe chest injuries. With an estimated mortality rate of 14–40%, pulmonary contusion plays a key role in determining whether an individual will die or suffer serious ill effects as the result of trauma. Pulmonary contusion is usually accompanied by other injuries. Although associated injuries are often the cause of death, pulmonary contusion is thought to cause death directly in a quarter to half of cases. Children are at especially high risk for the injury because the relative flexibility of their bones prevents the chest wall from absorbing force from an impact, causing it to be transmitted instead to the lung. Pulmonary contusion is associated with complications including pneumonia and acute respiratory distress syndrome, and it can cause long-term respiratory disability.

### **Classification**



The alveoli

Pulmonary contusion and laceration are injuries to the lung tissue. Pulmonary laceration, in which lung tissue is torn or cut, differs from pulmonary contusion in that the former involves disruption of the macroscopic architecture of the lung, while the latter does not. When lacerations fill with blood, the result is pulmonary hematoma, a collection of blood within the lung tissue. Contusion involves hemorrhage in the alveoli (tiny air-filled sacs responsible for absorbing oxygen), but a hematoma is a discrete clot of blood not interspersed with lung tissue. A collapsed lung can result when the pleural cavity (the space outside the lung) accumulates blood (hemothorax) or air (pneumothorax) or both (hemopneumothorax). These conditions do not inherently involve damage to the lung tissue itself, but they may be associated with it. Injuries to the chest wall are also distinct from but may be associated with lung injuries. Chest wall injuries include rib fractures and flail chest, in which multiple ribs are broken so that a segment of the ribcage is detached from the rest of the chest wall and moves independently.

### ***Signs and symptoms***

Presentation may be subtle; people with mild contusion may have no symptoms at all. However, pulmonary contusion is frequently associated with signs (objective indications) and symptoms (subjective states), including those indicative of the lung injury itself and of accompanying injuries. Because gas exchange is impaired, signs of low blood oxygen saturation, such as low concentrations of oxygen in arterial blood gas and cyanosis (bluish color of the skin and mucous membranes) are commonly associated. Dyspnea (painful breathing or difficulty breathing) is commonly seen, and tolerance for exercise may be lowered. Rapid breathing and a rapid heart rate are other signs. With more severe contusions, breath sounds heard through a stethoscope may be decreased, or rales (an abnormal crackling sound in the chest accompanying breathing) may be present. People with severe contusions may have bronchorrhea (the production of watery sputum). Wheezing and coughing are other signs. Coughing up blood or bloody sputum is present in up to half of cases. Cardiac output (the volume of blood pumped by the heart) may be reduced, and hypotension (low blood pressure) is frequently present. The area of the chest wall near the contusion may be tender or painful due to associated chest wall injury.

Signs and symptoms take time to develop, and as many as half of cases are asymptomatic at the initial presentation. The more severe the injury, the more quickly symptoms become apparent. In severe cases, symptoms may occur as quickly as three or four hours after the trauma. Hypoxemia (low oxygen concentration in the arterial blood) typically becomes progressively worse over 24–48 hours after injury. In general, pulmonary contusion tends to worsen slowly over a few days, but it may also cause rapid deterioration or death if untreated.

## **Causes**



Motor vehicle accidents are the most common cause of pulmonary contusion

Pulmonary contusion, which occurs in 25–35% of all blunt chest trauma, is usually caused by the rapid deceleration that results when the moving chest strikes a fixed object. About 70% of cases result from motor vehicle collisions, most often when the chest strikes the inside of the car. Falls, assaults, and sports injuries are other causes. Pulmonary contusion can also be caused by explosions; the organs most vulnerable to blast injuries are those that contain gas, such as the lungs. Blast lung is severe pulmonary contusion, bleeding, or edema with damage to alveoli and blood vessels, or a combination of these. This is the primary cause of death among people who initially survive an explosion.

In addition to blunt trauma, penetrating trauma can cause pulmonary contusion. Contusion resulting from penetration by a rapidly moving projectile usually surrounds the path along which the projectile traveled through the tissue. The pressure wave forces tissue out of the way, creating a temporary cavity; the tissue readily moves back into place, but it is hurt. Pulmonary contusions that accompany gun and knife wounds are not usually severe enough to have a major effect on outcome; penetrating trauma causes less widespread lung damage than does blunt trauma. An exception is shotgun wounds, which can seriously damage large areas of lung tissue through a blast injury mechanism.

## **Mechanism**

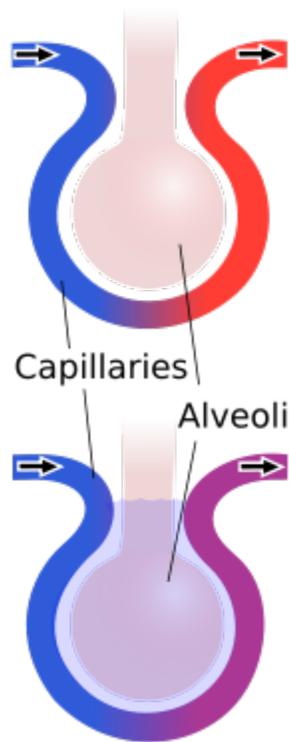
The physical processes behind pulmonary contusion are poorly understood. However, it is known that lung tissue can be crushed when the chest wall bends inward on impact. Three other possible mechanisms have been suggested: the inertial effect, the spalling effect, and the implosion effect.

- In the **inertial effect**, the lighter alveolar tissue is sheared from the heavier hilar structures, an effect similar to diffuse axonal injury in head injury. It results from the fact that different tissues have different densities, and therefore different rates of acceleration or deceleration.
- In the **spalling effect**, lung tissue bursts or is sheared where a shock wave meets the lung tissue, at interfaces between gas and liquid. The alveolar walls form such a gas-liquid interface with the air in the alveoli. The spalling effect occurs in areas with large differences in density; particles of the denser tissue are spalled (thrown) into the less dense particles.
- The **implosion effect** occurs when a pressure wave passes through a tissue containing bubbles of gas: the bubbles first implode, then rebound and expand beyond their original volume. The air bubbles cause many tiny explosions, resulting in tissue damage; the overexpansion of gas bubbles stretches and tears alveoli. This effect is thought to occur microscopically when the pressure in the airways increases sharply.

Contusion usually occurs on the lung directly under the site of impact, but, as with traumatic brain injury, a contrecoup contusion may occur at the site opposite the impact as well. A blow to the front of the chest may cause contusion on the back of the lungs because a shock wave travels through the chest and hits the curved back of the chest wall; this reflects the energy onto the back of the lungs, concentrating it. (A similar mechanism may occur at the front of the lungs when the back is struck.)

The amount of energy transferred to the lung is determined in a large part by the compliance (flexibility) of the chest wall. Children's chests are more flexible because their ribs are more elastic and there is less ossification of their intercostal cartilage. Therefore, their chest walls bend, absorbing less of the force and transmitting more of it to the underlying organs. An adult's more bony chest wall absorbs more of the force itself rather than transmitting it. Thus children commonly get pulmonary contusions without fractures overlying them, while elderly people are more likely to suffer fractures than contusions. One study found that pulmonary contusions were accompanied by fractures 62% of the time in children and 80% of the time in adults.

## ***Pathophysiology***



Normally, oxygen and carbon dioxide diffuse across the capillary and alveolar membranes and the interstitial space (top). Fluid impairs this diffusion, resulting in less oxygenated blood (bottom).

Pulmonary contusion results in bleeding and fluid leakage into lung tissue, which can become stiffened and lose its normal elasticity. The water content of the lung increases over the first 72 hours after injury, potentially leading to frank pulmonary edema in more serious cases. As a result of these and other pathological processes, pulmonary contusion progresses over time and can cause hypoxia (insufficient oxygen).

### **Bleeding and edema**

In contusions, torn capillaries leak fluid into the tissues around them. The membrane between alveoli and capillaries is torn; damage to this capillary–alveolar membrane and small blood vessels causes blood and fluids to leak into the alveoli and the interstitial space (the space surrounding cells) of the lung. With more severe trauma, there is a greater amount of edema, bleeding, and tearing of the alveoli. Pulmonary contusion is characterized by microhemorrhages (tiny bleeds) that occur when the alveoli are traumatically separated from airway structures and blood vessels. Blood initially collects in the interstitial space, and then edema occurs by an hour or two after injury. An area of bleeding in the contused lung is commonly surrounded by an area of edema. In normal gas exchange, carbon dioxide diffuses across the endothelium of the capillaries, the interstitial space, and across the alveolar epithelium; oxygen diffuses in the other

direction. Fluid accumulation interferes with gas exchange, and can cause the alveoli to fill with proteins and collapse due to edema and bleeding. The larger the area of the injury, the more severe respiratory compromise will be.

## **Consolidation and collapse**

Pulmonary contusion can cause parts of the lung to consolidate, alveoli to collapse, and atelectasis (partial or total lung collapse) to occur. Consolidation occurs when the parts of the lung that are normally filled with air fill with material from the pathological condition, such as blood. Over a period of hours after the injury, the alveoli in the injured area thicken and may become consolidated. A decrease in the amount of surfactant produced also contributes to the collapse and consolidation of alveoli; inactivation of surfactant increases their surface tension. Reduced production of surfactant can also occur in surrounding tissue that was not originally injured.

Inflammation of the lungs, which can result when components of blood enter the tissue due to contusion, can also cause parts of the lung to collapse. Macrophages, neutrophils, and other inflammatory cells and blood components can enter the lung tissue and release factors that lead to inflammation, increasing the likelihood of respiratory failure. In response to inflammation, excess mucus is produced, potentially plugging parts of the lung and leading to their collapse. Even when only one side of the chest is injured, inflammation may also affect the other lung. Uninjured lung tissue may develop edema, thickening of the septa of the alveoli, and other changes. If this inflammation is severe enough, it can lead to dysfunction of the lungs like that seen in acute respiratory distress syndrome.

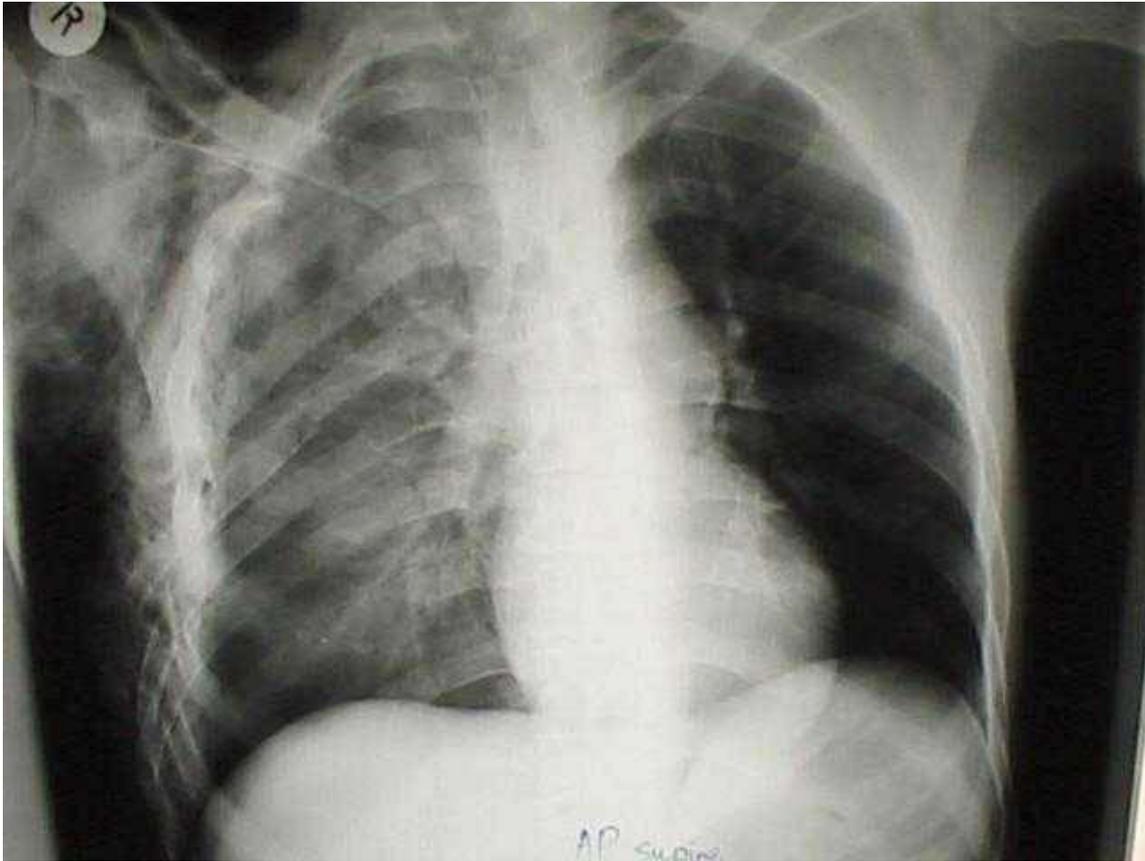
## **Ventilation/perfusion mismatch**

Normally, the ratio of ventilation to perfusion is about one-to-one; the volume of air entering the alveoli (ventilation) is about equal to that of blood in the capillaries around them (perfusion). This ratio is reduced in pulmonary contusion; fluid-filled alveoli cannot fill with air, oxygen does not fully saturate the hemoglobin, and the blood leaves the lung without being fully oxygenated. Insufficient inflation of the lungs, which can result from inadequate mechanical ventilation or an associated injury such as flail chest, can also contribute to the ventilation/perfusion mismatch. As the mismatch between ventilation and perfusion grows, blood oxygen saturation is reduced. Pulmonary hypoxic vasoconstriction, in which blood vessels near the hypoxic alveoli constrict (narrow their diameter) in response to the lowered oxygen levels, can occur in pulmonary contusion. The vascular resistance increases in the contused part of the lung, leading to a decrease in the amount of blood that flows into it, directing blood to better-ventilated areas. Although reducing blood flow to the unventilated alveoli is a way to compensate for the fact that blood passing unventilated alveoli is not oxygenated, the oxygenation of the blood remains lower than normal. If it is severe enough, the hypoxemia resulting from fluid in the alveoli cannot be corrected just by giving supplemental oxygen; this problem is the cause of a large portion of the fatalities that result from trauma.

## **Diagnosis**

To diagnose pulmonary contusion, health professionals use clues from a physical examination, information about the event that caused the injury, and radiography. Laboratory findings may also be used; for example, arterial blood gasses may show insufficient oxygen and excessive carbon dioxide even in someone receiving supplemental oxygen. However, blood gas levels may show no abnormality early in the course of pulmonary contusion.

## **X-ray**



A chest X-ray showing right sided pulmonary contusion associated with rib fractures and subcutaneous emphysema

Chest X-ray is the most common method used for diagnosis, and may be used to confirm a diagnosis already made using clinical signs. Consolidated areas appear white on an X-ray film. Contusion is not typically restricted by the anatomical boundaries of the lobes or segments of the lung. The X-ray appearance of pulmonary contusion is similar to that of aspiration, and the presence of hemothorax or pneumothorax may obscure the contusion on a radiograph. Signs of contusion that progress after 48 hours post-injury are likely to be actually due to aspiration, pneumonia, or ARDS.

Although chest radiography is an important part of the diagnosis, it is often not sensitive enough to detect the condition early after the injury. In a third of cases, pulmonary contusion is not visible on the first chest radiograph performed. It takes an average of six hours for the characteristic white regions to show up on a chest X-ray, and the contusion may not become apparent for 48 hours. When a pulmonary contusion is apparent in an X-ray, it suggests that the trauma to the chest was severe and that a CT scan might reveal other injuries that were missed with X-ray.

### **Computed tomography**



A chest CT scan revealing pulmonary contusions, pneumothorax, and pseudocysts

Computed tomography (CT scanning) is a more sensitive test for pulmonary contusion, and it can identify abdominal, chest, or other injuries that accompany the contusion. In one study, chest X-ray detected pulmonary contusions in 16.3% of people with serious blunt trauma, while CT detected them in 31.2% of the same people. Unlike X-ray, CT scanning can detect the contusion almost immediately after the injury. However, in both X-ray and CT a contusion may become more visible over the first 24–48 hours after trauma as bleeding and edema into lung tissues progress. CT scanning also helps determine the size of a contusion, which is useful in determining whether a patient needs mechanical ventilation; a larger volume of contused lung on CT scan is associated with an increased likelihood that ventilation will be needed. CT scans also help differentiate between contusion and pulmonary hematoma, which may be difficult to tell apart

otherwise. However, pulmonary contusions that are visible on CT but not chest X-ray are usually not severe enough to affect outcome or treatment.

## Ultrasound



An ultrasound image showing early pulmonary contusion, at this moment not visible on radiography. Interstitial syndromes are expressed with the vertical white lines, the "B-lines".

Pulmonary ultrasound, performed at the bedside or on the accident scene, is being explored as a diagnosis for pulmonary contusion. Its use is still not widespread, being limited to facilities which are comfortable with its use for other applications, like pneumothorax, airway management, and hemothorax. Accuracy has been found to be comparable to CT scanning.

## Prevention

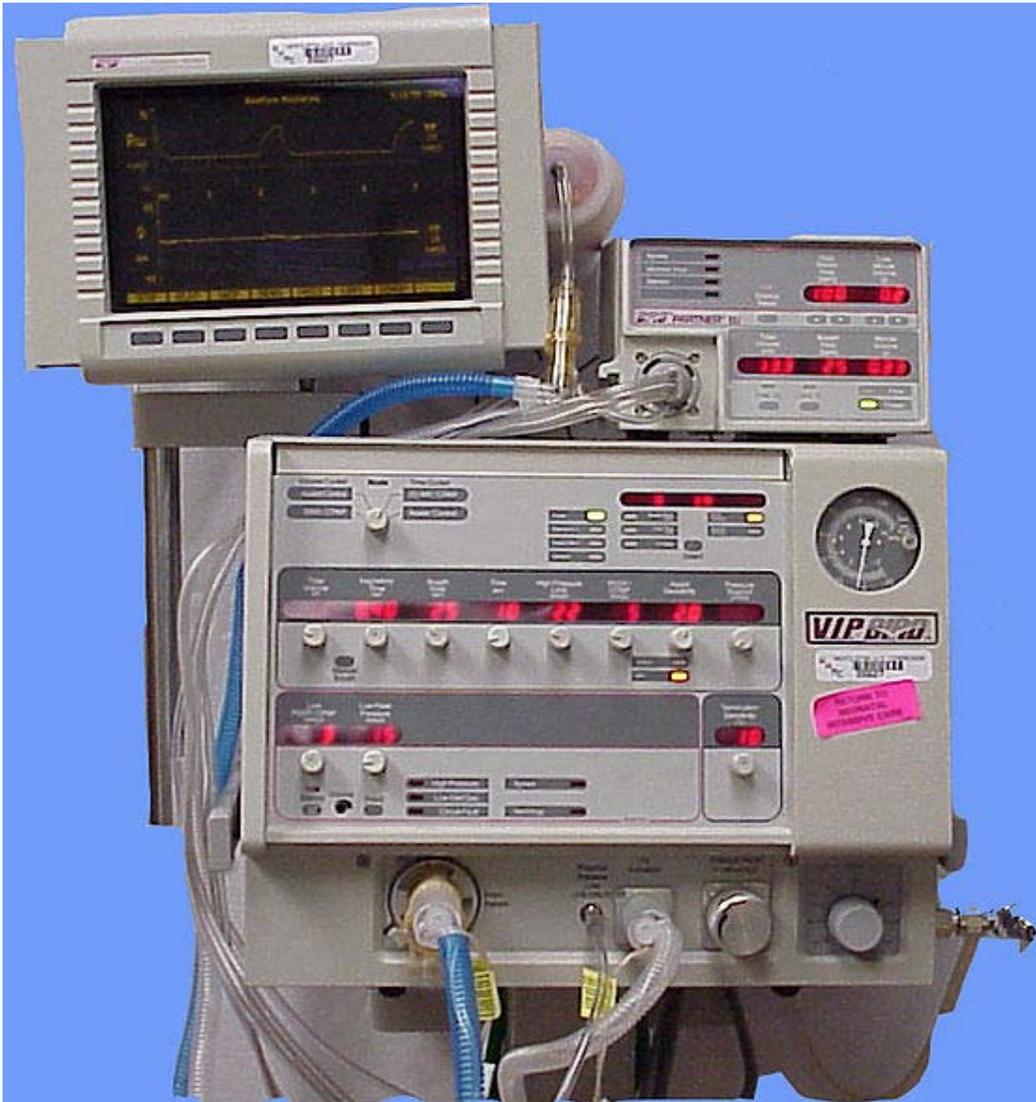
Prevention of pulmonary contusion is similar to that of other chest trauma. Airbags in combination with seat belts can protect vehicle occupants by preventing the chest from striking the interior of the vehicle during a collision, and by distributing forces involved in the crash more evenly across the body. However, in rare cases, an airbag causes pulmonary contusion in a person who is not properly positioned when it deploys. Child restraints such as carseats protect children in vehicle collisions from pulmonary contusion. Equipment exists for use in some sports to prevent chest and lung injury; for

example, in softball the catcher is equipped with a chest protector. Athletes who do not wear such equipment, such as basketball players, can be trained to protect their chests from impacts. Protective garments can also prevent pulmonary contusion in explosions. Although traditional body armor made from rigid plates or other heavy materials protects from projectiles generated by a blast, it does not protect against pulmonary contusion, because it does not prevent the blast's shock wave from being transferred to the lung. Special body armor has been designed for military personnel at high risk for blast injuries; these garments can prevent a shock wave from being propagated across the chest wall to the lung, and thus protect wearers from blast lung injuries. These garments alternate layers of materials with high and low acoustic impedance (the product of a material's density and a wave's velocity through it) in order to "decouple" the blast wave, preventing its propagation into the tissues.

### ***Treatment***

No treatment is known to speed the healing of a pulmonary contusion; the main care is supportive. Attempts are made to discover injuries accompanying the contusion, to prevent additional injury, and to provide supportive care while waiting for the contusion to heal. Monitoring, including keeping track of fluid balance, respiratory function, and oxygen saturation using pulse oximetry is also required as the patient's condition may progressively worsen. Monitoring for complications such as pneumonia and acute respiratory distress syndrome is of critical importance. Treatment aims to prevent respiratory failure and to ensure adequate blood oxygenation. Supplemental oxygen can be given and it may be warmed and humidified. When the contusion does not respond to other treatments, extracorporeal membranous oxygenation may be used, pumping blood from the body into a machine that oxygenates it and removes carbon dioxide prior to pumping it back in.

## Ventilation



Mechanical ventilation may be required if pulmonary contusion causes inadequate oxygenation.

Positive pressure ventilation, in which air is forced into the lungs, is needed when oxygenation is significantly impaired. Noninvasive positive pressure ventilation including continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP), may be used to improve oxygenation and treat atelectasis. In both, air is blown into the airways at a prescribed pressure via a mask fitted tightly to the face; in BiPAP the pressure changes between inhalation and exhalation, while in CPAP the pressure is the same during both. Noninvasive ventilation has advantages over invasive methods because it does not carry the risk of infection that intubation does, and it allows normal coughing, swallowing, and speech. However, the technique may cause complications; it may force air into the stomach or cause aspiration of stomach contents, especially when level of consciousness is decreased.

People with signs of inadequate respiration or oxygenation may need to be intubated and mechanically ventilated. Mechanical ventilation aims to reduce pulmonary edema and increase oxygenation. Ventilation can reopen collapsed alveoli, but it is harmful for them to be repeatedly opened, and positive pressure ventilation can also damage the lung by overinflating it. Intubation is normally reserved for when respiratory problems occur, but most significant contusions do require intubation, and it may be done early in anticipation of this need. People with pulmonary contusion who are especially likely to need ventilation include those with prior severe lung disease or kidney problems; the elderly; those with a lowered level of consciousness; those with low blood oxygen or high carbon dioxide levels; and those who are going to be operated on and need anesthesia.

Pulmonary contusion or its complications such as acute respiratory distress syndrome may cause lungs to lose compliance (stiffen), so higher pressures may be needed to give normal amounts of air and oxygenate the blood adequately. Positive end-expiratory pressure (PEEP), which delivers air at a given pressure at the end of the expiratory cycle, can reduce edema and keep alveoli from collapsing. PEEP is considered necessary with mechanical ventilation; however, if the pressure is too great it can expand the size of the contusion and injure the lung. When the compliance of the injured lung differs significantly from that of the uninjured one, the lungs can be ventilated independently with two ventilators in order to deliver air at different pressures; this helps avoid injury from overinflation while providing adequate ventilation.

## **Fluid therapy**

The administration of fluid therapy in individuals with pulmonary contusion is controversial. Excessive fluid in the circulatory system (hypervolemia) can worsen hypoxia because it can cause fluid leakage from injured capillaries (pulmonary edema), which are more permeable than normal. However, low blood volume (hypovolemia) resulting from insufficient fluid has an even worse impact, potentially causing hypovolemic shock; for people who have lost large amounts of blood, fluid resuscitation is necessary. A lot of the evidence supporting the idea that fluids should be withheld from people with pulmonary contusion came from animal studies, not clinical trials with humans; human studies have had conflicting findings on whether fluid resuscitation worsens the condition. For people who do require large amounts of intravenous fluid, a catheter may be placed in the pulmonary artery to measure the pressure within it. Measuring pulmonary artery pressure allows the clinician to give enough fluids to prevent shock without exacerbating edema. Diuretics, drugs that increase urine output to reduce excessive fluid in the system, can be used when fluid overload does occur. Furosemide, a diuretic used in the treatment of pulmonary contusion, also relaxes the smooth muscle in the veins of the lungs, thereby decreasing pulmonary venous resistance and reducing the pressure in the pulmonary capillaries.

## **Supportive care**

Retaining secretions in the airways can worsen hypoxia and lead to infections. Thus, an important part of treatment is pulmonary toilet, the use of suction, deep breathing,

coughing, and other methods to remove material such as mucus and blood from the airways. Chest physical therapy makes use of techniques such as breathing exercises, stimulation of coughing, suctioning, percussion, movement, vibration, and drainage to rid the lungs of secretions, increase oxygenation, and expand collapsed parts of the lungs. People with pulmonary contusion, especially those who do not respond well to other treatments, may be positioned with the uninjured lung lower than the injured one to improve oxygenation. Inadequate pulmonary toilet can result in pneumonia. People who do develop infections are given antibiotics. No studies have yet shown a benefit of using antibiotics as a preventative measure before infection occurs, although some doctors do recommend prophylactic antibiotic use even without scientific evidence of its benefit. However, this can cause the development of antibiotic resistant strains of bacteria, so giving antibiotics without a clear need is normally discouraged. For people who are at especially high risk of developing infections, the sputum can be cultured to test for the presence of infection-causing bacteria; when they are present, antibiotics are used.

Pain control is another means to facilitate the elimination of secretions. A chest wall injury can make coughing painful, increasing the likelihood that secretions will accumulate in the airways. Chest injuries also contribute to hypoventilation (inadequate breathing) because the chest wall movement involved in breathing adequately is painful. Insufficient expansion of the chest may lead to atelectasis, further reducing oxygenation of the blood. Analgesics (pain medications) can be given to reduce pain. Injection of anesthetics into nerves in the chest wall, called nerve blockade, is another approach to pain management; this does not depress respiration the way some pain medications can.

## ***Prognosis***



This CT scan, taken 22 days after pulmonary contusion with major chest trauma, shows that the contusion has completely resolved.

Pulmonary contusion usually resolves itself without causing permanent complications; however it may also have long-term ill effects on respiratory function. Most contusions resolve in five to seven days after the injury. Signs detectable by radiography are usually

gone within 10 days after the injury—when they are not, other conditions, such as pneumonia, are the likely cause. Chronic lung disease correlates with the size of the contusion and can interfere with an individual's ability to return to work. Fibrosis of the lungs can occur, resulting in dyspnea (shortness of breath), low blood oxygenation, and reduced functional residual capacity for as long as six years after the injury. As late as four years post-injury, decreased functional residual capacity has been found in most pulmonary contusion patients studied. During the six months after pulmonary contusion, up to 90% of people suffer difficulty breathing. In some cases, dyspnea persists for an indefinite period. Contusion can also permanently reduce the compliance of the lungs.

## Complications

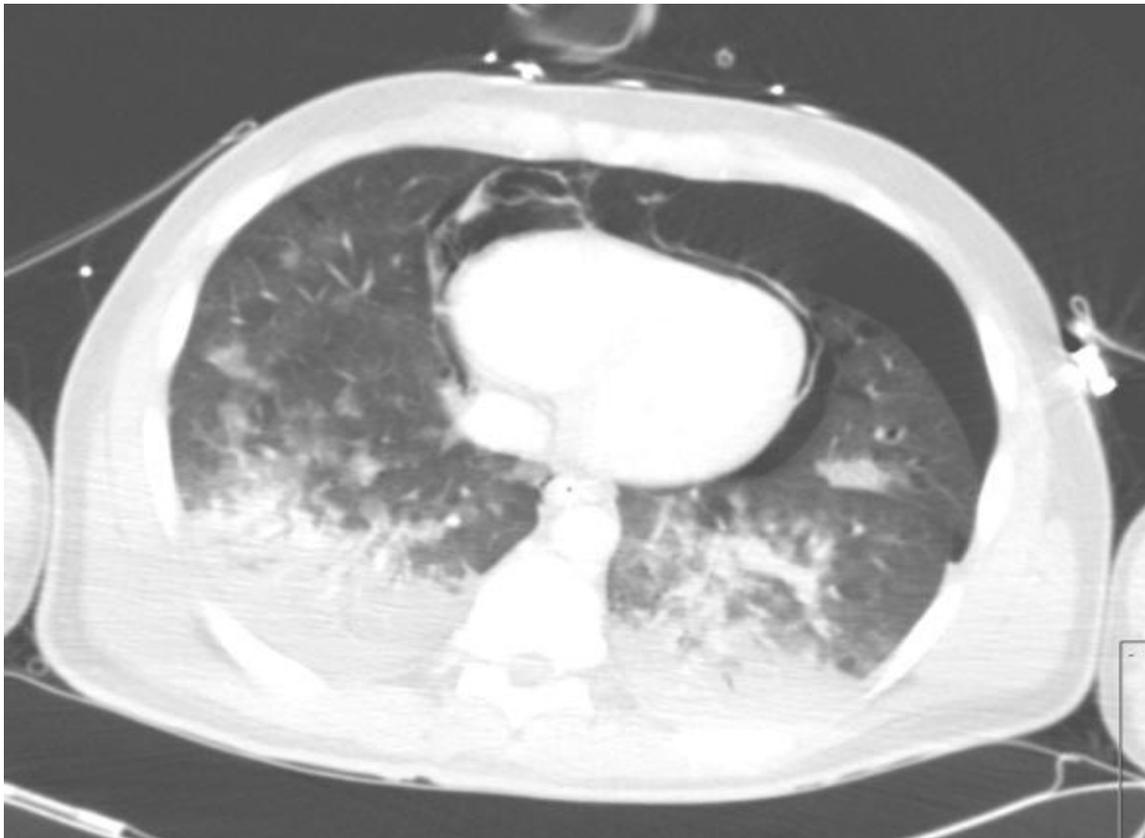


A chest X-ray showing acute respiratory distress syndrome

Pulmonary contusion can result in respiratory failure—about half of such cases occur within a few hours of the initial trauma. Other severe complications, including infections and acute respiratory distress syndrome (ARDS) occur in up to half of cases. Elderly people and those who have heart, lung, or kidney disease prior to the injury are more likely to stay longer in hospital and have complications from the injury. Complications occur in 55% of people with heart or lung disease and 13% of those without. Of people with pulmonary contusion alone, 17% develop ARDS, while 78% of people with at least two additional injuries develop the condition. A larger contusion is associated with an increased risk. In one study, 82% of people with 20% or more of the lung volume affected developed ARDS, while only 22% of people with less than 20% did so.

Pneumonia, another potential complication, develops in as many as 20% of people with pulmonary contusion. Contused lungs are less able to remove bacteria than uninjured lungs, predisposing them to infection. Intubation and mechanical ventilation further increase the risk of developing pneumonia; the tube is passed through the nose or mouth into the airways, potentially tracking bacteria from the mouth or sinuses into them. Also, intubation prevents coughing, which would clear bacteria-laden secretions from the airways, and secretions pool near the tube's cuff and allow bacteria to grow. The sooner the endotracheal tube is removed, the lower the risk of pneumonia, but if it is removed too early and has to be put back in, the risk of pneumonia rises. People who are at risk for pulmonary aspiration (e.g. those with lowered level of consciousness due to head injuries) are especially likely to get pneumonia. As with ARDS, the chances of developing pneumonia increase with the size of the contusion. Children and adults have been found to have similar rates of complication with pneumonia and ARDS.

### **Associated injuries**



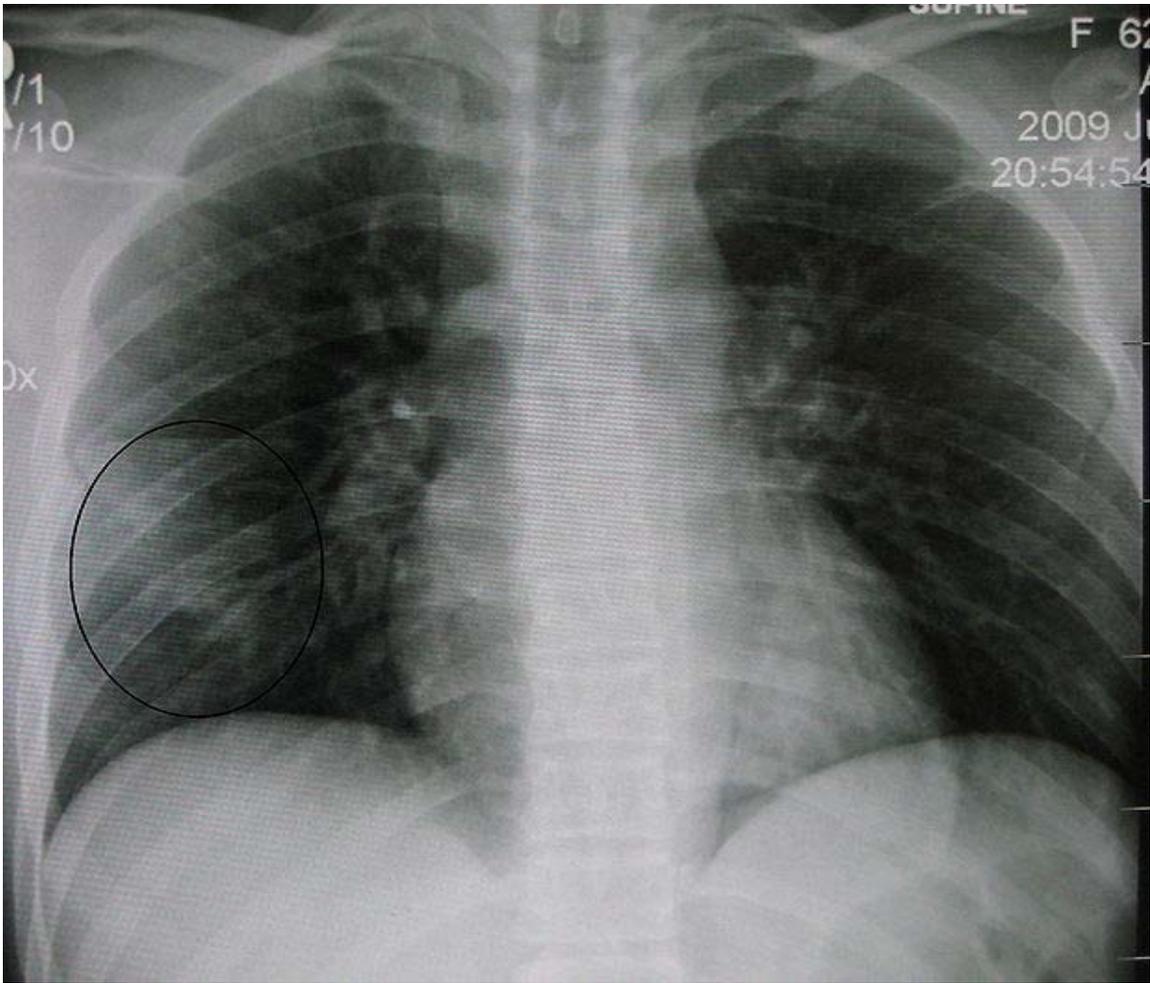
Severe pulmonary contusion with pneumothorax and hemothorax following severe chest trauma

A large amount of force is required to cause pulmonary contusion; a person injured with such force is likely to have other types of injuries as well, and pulmonary contusion can be used to gauge the severity of trauma. Up to three quarters of cases are accompanied by other chest injuries, the most common of these being hemothorax and pneumothorax.

Flail chest is usually associated with pulmonary contusion, and the contusion, rather than the chest wall injury, is often the main cause of respiratory failure in people with these injuries. Other indications of thoracic trauma may be associated, including fracture of the sternum and bruising of the chest wall. Over half of fractures of the scapula are associated with pulmonary contusion. The contusion is frequently found underlying fracture sites. When accompanied by a fracture, it is usually concentrated into a specific location—the contusion is more diffuse when there is no fracture. Pulmonary lacerations may result from the same blunt or penetrating forces that cause pulmonary contusion. Lacerations can result in pulmonary hematomas; these are reported to develop in 4–11% of pulmonary contusions.

### ***Epidemiology***

Pulmonary contusion is found in 30–75% of severe cases of chest injury, making it the most common serious injury to occur in association with thoracic trauma. Of people who have multiple injuries with an injury severity score of over 15, pulmonary contusion occurs in about 17%. It is difficult to determine the death rate (mortality) because pulmonary contusion rarely occurs by itself. Usually, deaths of people with pulmonary contusion result from other injuries, commonly traumatic brain injury. It is controversial whether pulmonary contusion with flail chest is a major factor in mortality on its own or whether it merely contributes to mortality in people with multiple injuries. The mortality rate of pulmonary contusion is estimated to range from 14–40%, depending on the severity of the contusion itself and on associated injuries. When the contusions are small, they do not normally increase the chance of death or poor outcome for people with blunt chest trauma; however, these chances increase with the size of the contusion. One study found that 35% of people with multiple significant injuries including pulmonary contusion die. In another study, 11% of people with pulmonary contusion alone died, while the number rose to 22% in those with additional injuries. An accompanying flail chest increases the morbidity and mortality to more than twice that of pulmonary contusion alone. Pulmonary contusion is thought to be the direct cause of death in a quarter to a half of people with polytrauma who die.



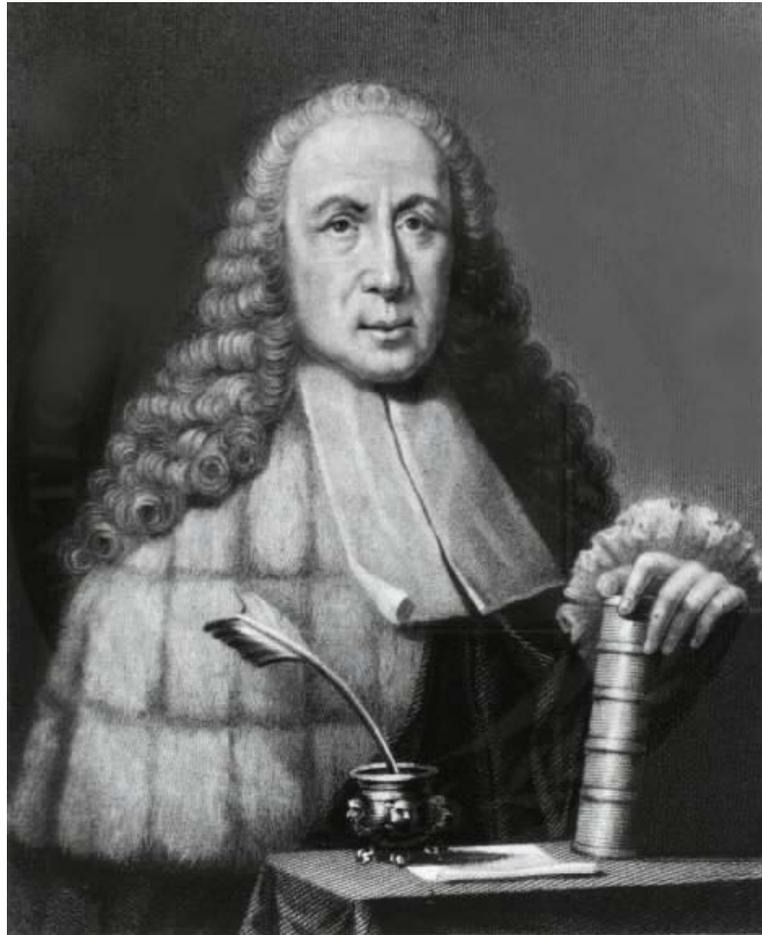
A right-sided pulmonary contusion post blunt chest trauma with increased opacity just below the horizontal fissure

Pulmonary contusion is the most common cause of death among vehicle occupants involved in accidents, and it is thought to contribute significantly in about a quarter of deaths resulting from vehicle collisions. As vehicle use has increased, so has the number of auto accidents, and with it the number of chest injuries. However an increase in the number of airbags installed in modern cars may be decreasing the incidence of pulmonary contusion. Use of child restraint systems has brought the approximate incidence of pulmonary contusion in children in vehicle accidents from 22% to 10%.

Since their chest walls are more flexible, children are more vulnerable to pulmonary contusion than adults are, and it is more common in children than in adults for that reason. Children in forceful impacts suffer twice as many pulmonary contusions as adults with similar injury mechanisms, yet have proportionately fewer rib fractures. Pulmonary contusion has been found in 53% of children with significant chest injuries (those requiring hospitalization). The rates of certain types of injury mechanisms differ between children and adults; for example, children are more often hit by cars when they are pedestrians. Differences in the bodies of children and adults also lead to different

manifestations of pulmonary contusion and associated injuries; for example, children have less body mass, so the same force is more likely to lead to trauma to multiple body systems. Some differences in children's physiology might be advantageous (for example they are less likely to have other medical conditions), and thus they have been predicted to have a better outcome. However, despite these differences, children with pulmonary contusion have similar mortality rates to adults.

## **History**



Giovanni Battista Morgagni, credited with having first described lung trauma without chest wall trauma

In 1761, the Italian anatomist Giovanni Battista Morgagni was first to describe a lung injury that was not accompanied by injury to the chest wall overlying it. Nonetheless, it was the French military surgeon Guillaume Dupuytren who is thought to have coined the term *pulmonary contusion* in the 19th century. It still was not until the early 20th century that pulmonary contusion and its clinical significance began to receive wide recognition. With the use of explosives during World War I came many casualties with no external signs of chest injury but with significant bleeding in the lungs. Studies of World War I injuries by D.R. Hooker showed that pulmonary contusion was an important part of the concussive injury that results from explosions.

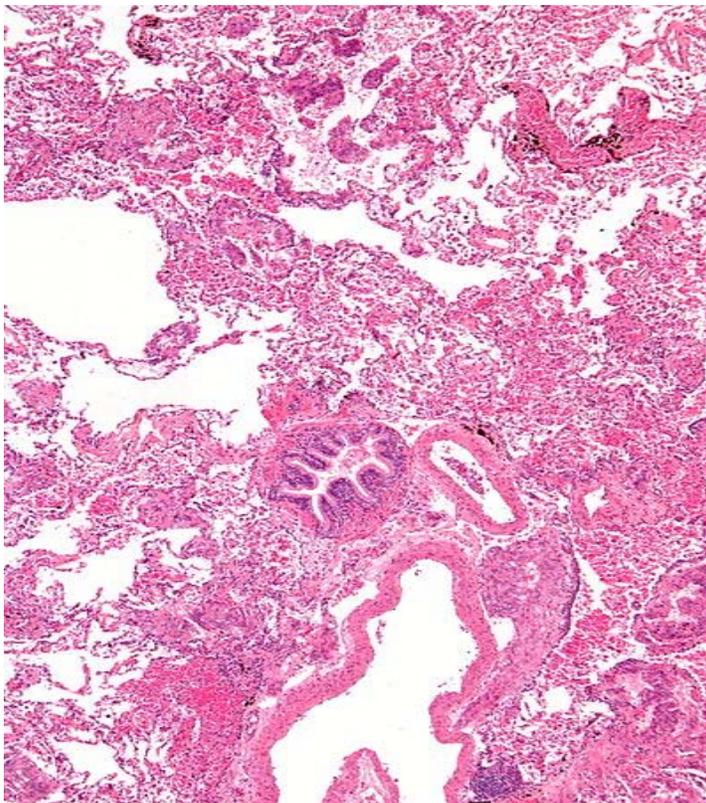
Pulmonary contusion received further attention during World War II, when the bombings of Britain caused blast injuries and associated respiratory problems in both soldiers and civilians. Also during this time, studies with animals placed at varying distances from a blast showed that protective gear could prevent lung injuries. These findings suggested that an impact to the outside of the chest wall was responsible for the internal lesions. In 1945, Buford and Burbank described what they called "wet lung", in which the lungs accumulated fluid and were simultaneously less able to remove it. They attributed the respiratory failure often seen in blunt chest trauma in part to excessive fluid resuscitation, and the question of whether and how much to administer fluids has remained controversial ever since.

During the Vietnam War, combat again provided the opportunity for study of pulmonary contusion; research during this conflict played an important role in the development of the modern understanding of its treatment. The condition also began to be more widely recognized in a non-combat context in the 1960s, and symptoms and typical findings with imaging techniques such as X-ray were described. Before the 1960s, it was believed that the respiratory insufficiency seen in flail chest was due to "paradoxical motion" of the flail segment of the chest wall (the flail segment moves in the opposite direction as the chest wall during respiration), so treatment was aimed at managing the chest wall injury, not the pulmonary contusion. For example, positive pressure ventilation was used to stabilize the flail segment from within the chest. It was first proposed in 1965 that this respiratory insufficiency is most often due to injury of the lung rather than to the chest wall, and a group led by J.K. Trinkle confirmed this hypothesis in 1975. Hence the modern treatment prioritizes the management of pulmonary contusion. Animal studies performed in the late 1960s and 1970s shed light on the pathophysiological processes involved in pulmonary contusion.

## Chapter 4

# Lymphangioliomyomatosis

### Lymphangioliomyomatosis



Micrograph of lymphangioliomyomatosis. H&E stain.

<b>ICD-O:</b>	9174/1
<b>OMIM</b>	606690
<b>DiseasesDB</b>	30755
<b>eMedicine</b>	med/1348 radio/415
<b>MeSH</b>	D018192

**Lymphangiomyomatosis (LAM)** is a rare lung disease that results in a proliferation of disorderly smooth muscle growth (leiomyoma) throughout the bronchioles, alveolar septa, perivascular spaces, and lymphatics, resulting in the obstruction of small airways (leading to pulmonary cyst formation and pneumothorax) and lymphatics (leading to chylous pleural effusion). LAM occurs in a sporadic form, which only affects females, who are usually of childbearing age. LAM also occurs in patients who have tuberous sclerosis.

## **Cause**

Sporadic LAM almost always affects women.

The proliferating smooth muscle that occurs in the type of LAM seen in patients with tuberous sclerosis (TSC-LAM) has been shown to represent clones of the smooth muscle in those patients' renal angiomyolipomas. Thus it is believed to represent metastases of this "benign" tumor. There is a female preponderance to TSC-LAM. LAM occurs almost exclusively in women. The average age at onset of symptoms is approximately 34 years (5–7). The first symptoms of the disease can occur before an abnormality is detectable with chest plain radiographs or pulmonary function tests; even when such abnormalities exist, the disease may be initially misdiagnosed. There is often a delay between the onset of symptoms and correct diagnosis.

LAM commonly manifests as exertional dyspnea and recurrent pneumothorax. During the course of the illness, there may be nonproductive cough, hemoptysis, chylous pleural effusion, or chylous ascites (3,5). Obstruction of pulmonary venules causes vascular congestion and hemoptysis, and lymphatic obstruction leads to chylothorax and chylous ascites.

The clinical course of patients with LAM shows considerable variation. The disease is believed to be slowly progressive, leading to respiratory failure and death. The 10-year survival from the start of symptoms in a study at our institution was 49% (7), although reported figures range from an 8.5-year survival probability of 38% to a 10-year survival of 79% (8). Differences in survival rates may be due to improvements in diagnosis, particularly regarding the contribution of high-resolution CT, and do not mean that the progression of the disease has changed substantially. Diagnosis of mild asymptomatic forms may also have contributed to the longer survival rates (4).

Spirometry studies in LAM patients demonstrate chronic airway obstruction with increased lung volume and decreased CO<sub>2</sub> diffusion. The radiologic finding of an interstitial pattern with these spirometric results in a young woman narrows the differential diagnosis to some forms of emphysema, Langerhans cell histiocytosis, and sarcoidosis. The information provided by HRCT is essential for differentiating LAM from these conditions.

Numerous therapeutic strategies have been described to treat LAM (4). In light of the reports of clinical worsening of the disease during pregnancy and with use of exogenous

estrogens, many clinicians have applied therapeutic hormone manipulation. Antiestrogen therapy, first used in the early 1980s, consists of surgical castration by oophorectomy or administration of tamoxifen, progesterone, and gonadotropin-releasing hormone agonist or luteinizing hormone–releasing hormone (3,5). Several studies have reported beneficial effects of antiestrogen hormone therapies for LAM, but careful scrutiny of some of these studies reveals that the treatment improved the chylothorax or chylous ascites, whereas pulmonary involvement seemed to remain stationary or to progress. Since lung transplantation has become available for patients with poor response to therapies, certain treatments must be used with caution. In fact, castration does not clearly demonstrate a beneficial effect on the course of the disease, and the long-term effects of castration, particularly in the postoperative period of lung transplantation, can increase bone complications.

In most cases, chylothorax should be managed conservatively. Chylothorax usually appears early in the course of the disease, when the patient's functional status is good. Early application of surgical techniques such as pleural abrasion, pleurodesis, or pleurectomy must be avoided because these treatments might limit future lung transplantation. Medical treatment includes tamoxifen, progesterone, and, in some cases, a low-fat diet (4,5).

When the patient's functional status declines, bilateral lung transplantation is the best therapeutic option. The guidelines indicating transplantation include progression despite medical treatment, forced expiratory volume in 1 second (FEV1)/forced vital capacity ratio of less than 50%, total lung capacity of greater than 130%, and FEV1 of less than 30%. In the largest published series of lung transplantations in LAM patients, the average FEV1 at the time of evaluation for the procedure was 24%.

Common postoperative complications of lung transplantation are bacterial, viral, and fungal infections; acute rejection episodes; and chronic rejection. Complications specific to LAM are pneumothorax of the native lung after single-lung transplantation, chylothorax, recurrence of LAM, and abdominal complications Clinics:

#### Clinical Features

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## ***Prognosis***

Exact data on survival rates are difficult to collect because LAM is often misdiagnosed as asthma or other more common diseases, and may not be correctly identified until it is in an advanced condition. A comprehensive study of all known British LAM patients found that out of 21 patients that had been observed for 15 years or more since diagnosis, 18 were still alive; and 11 of 12 patients that had been observed for 20 years or more were alive, however, no data is available on respiratory disability.

## ***Complications***

- Worsening pulmonary insufficiency
- Pneumothorax, secondary to rupture of a cyst into the pleural space
- Chylous pleural effusions

## ***Treatment***

The association of LAM with women of childbearing age suggests that hormonal stimulation plays a role in the disease process, and several approaches to treatment involve diminishing the effect of estrogen. At one time or another, therapeutic approaches have included

- progesterone
- oophorectomy
- tamoxifen
- gonadotropin-releasing hormone (GnRH) agonists
- androgen therapy

No therapy is clearly efficacious, and all have undesirable side-effects. There is some evidence which shows that tamoxifen may actually cause worsening of LAM in some patients.

When pulmonary function deteriorates to the point where oxygenation is inadequate, lung transplantation is usually performed. Following lung transplant (usually unilateral), LAM patients have Kaplan-Meier estimators (survival curves) similar to other lung transplant patients. Abnormal smooth muscle may, however, also proliferate in the transplanted lung.

A single case report of an apparent response to Doxycycline has recently been reported.

Sirolimus is being tested for the treatment of LAM. The MILES Trial (Multicenter International LAM Efficacy of Sirolimus Trial) is now underway. The first site, the University of Cincinnati, is open for enrollment. The National Institutes of Health will open enrollment soon. The MILES Trial is randomized, double-blinded, and placebo-controlled. The objective of the Trial is to determine if sirolimus has a beneficial effect on lung function in LAM patients.

## Chapter 5

# Obstructive Lung Disease

### Obstructive lung disease

MeSH

D008173

**Obstructive lung disease** is a category of respiratory disease characterized by airway obstruction.

MeSH includes the following in this category:

- Asthma
- Emphysema
- Bronchitis
- Chronic obstructive pulmonary disease

Cystic fibrosis is sometimes also included in this category.

FEV1/FVC ratio is usually decreased.

### Overview table

Following is an overview of the main obstructive lung diseases. *Chronic obstructive pulmonary disease* is mainly a combination of chronic bronchitis and emphysema, but may be more or less overlapping with all conditions.

Condition	Main site	Major changes	Causes	Symptoms
<b>Chronic bronchitis</b>	Bronchus	Hyperplasia and hypersecretion of mucus glands	Tobacco smoking and air pollutants	Productive cough
<b>Bronchiectasis</b>	Bronchus	Dilation and scarring of airways	Persistent severe infections	Cough, purulent sputum and fever
<b>Asthma</b>	Bronchus	<ul style="list-style-type: none"><li>• Smooth muscle</li></ul>	Immunologic or	Episodic

		hyperplasia	idiopathic	wheezing, cough and dyspnea
		<ul style="list-style-type: none"> <li>Excessive mucus</li> <li>Inflammation</li> </ul>		
<b>Emphysema</b>	Acinus	Airspace enlargement and wall destruction	Tobacco smoking	Dyspnea
<b>Bronchiolitis</b> (subgroup of chronic bronchitis)	Bronchiole	Inflammatory scarring and bronchiole obliteration	Tobacco smoking and air pollutants	Cough, dyspnea

## Scope

### Chronic obstructive pulmonary disease

**Chronic obstructive pulmonary disease (COPD)**, also known as chronic obstructive airways disease (COAD) or chronic airflow limitation (CAL), is a group of illnesses characterised by airflow limitation that is not fully reversible. The flow of air into and out of the lungs is impaired. This can be measured with breathing devices such as a peak flow meter or by spirometry. The term COPD includes the conditions emphysema and chronic bronchitis although most patients with COPD have characteristics of both conditions to varying degrees. Asthma being a reversible obstruction of airways is often considered separately, but many COPD patients also have some degree of reversibility in their airways.

In COPD, there is an increase in airway resistance, shown by a decrease in the forced expiratory volume in 1 second (FEV1) measured by spirometry. COPD is defined as a forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) that is less than 0.7. The residual volume, the volume of air left in the lungs following full expiration, is often increased in COPD, as is the total lung capacity, while the vital capacity remains relatively normal. The increased total lung capacity (hyperinflation) can result in the clinical feature of a "barrel chest" - a chest with a large front-to-back diameter that occurs in some individuals with COPD. Hyperinflation can also be seen on a chest x-ray as a flattening of the diaphragm.

The most common cause of COPD is cigarette smoking. COPD is a gradually progressive condition and usually only develops after about 20 pack-years of smoking. COPD may also be caused by breathing in other particles and gases.

The diagnosis of COPD is established through spirometry although other pulmonary function tests can be helpful. A chest x-ray is often ordered to look for hyperinflation and rule out other lung conditions but the lung damage of COPD is not always visible on a chest x-ray. Emphysema, for example can only be seen on CT scan.

The main form of long term management involves the use of inhaled bronchodilators (specifically beta agonists and anticholinergics) and inhaled corticosteroids. Many

patients eventually require oxygen supplementation at home. In severe cases that are difficult to control, chronic treatment with oral corticosteroids may be necessary, although this is fraught with significant side-effects.

COPD is generally irreversible although lung function can partially recover if the patient stops smoking. Smoking cessation is an essential aspect of treatment. Pulmonary rehabilitation programmes involve intensive exercise training combined with education and are effective in improving shortness of breath. Severe emphysema has been treated with lung volume reduction surgery, with some success in carefully chosen cases. Lung transplantation is also performed for severe COPD in carefully chosen cases.

Alpha 1-antitrypsin deficiency is a fairly rare genetic condition that results in COPD (particularly emphysema) due to a lack of the antitrypsin protein which protects the fragile alveolar walls from protease enzymes released by inflammatory processes.

## **Asthma**

Asthma is an obstructive lung disease where the bronchial tubes (airways) are extra sensitive (hyperresponsive). The airways become inflamed and produce excess mucus and the muscles around the airways tighten making the airways narrower. Asthma is usually triggered by breathing in things in the air such as dust or pollen that produce an allergic reaction. It may be triggered by other things such as an upper respiratory tract infection, cold air, exercise or smoke. Asthma is a common condition and affects over 300 million people around the world. Asthma causes recurring episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.

Asthma is diagnosed by the characteristic pattern of symptoms.

A peak flow meter can record variations in the severity of asthma over time. Spirometry, a measurement of lung function, can provide an assessment of the severity, reversibility, and variability of airflow limitation, and help confirm the diagnosis of asthma.

Asthma is treated by identifying and removing the triggers that set it off, if possible. The main form of long term management involves the use of inhaled corticosteroids. Inhaled bronchodilators, particularly beta agonists are used to relieve and control symptoms by reducing muscle spasm around the airways. An alternative way to control mild asthma is with a leukotriene antagonist tablet.

## **Other obstructive lung diseases**

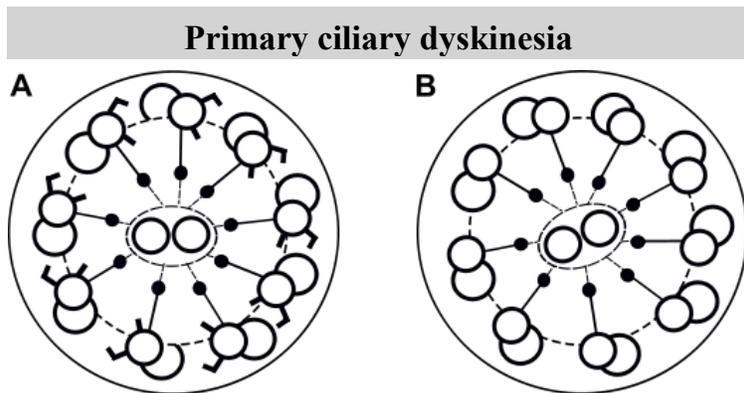
- Cystic fibrosis is an inherited disorder of the CFTR gene, a chloride ion channel. The lack of this channel causes reduced water content of secretions. This affects the mucus secreted as part of the lung's defence and creates sticky, viscous mucus. This makes the lungs more susceptible to infection, inflammation and mucous plugging.

- Bronchiectasis
- Bronchiolitis
- Allergic bronchopulmonary aspergillosis

In many parts of the world, the most common cause of obstructive lung disease is lung scarring after tuberculosis infection.

## Chapter 6

# Primary Ciliary Dyskinesia



Normal cilia (A) cilia in Kartagener's syndrome (B).

ICD-10	Q89.3*
ICD-9	759.3*
OMIM	244400 242650
DiseasesDB	7111 29887
eMedicine	med/1220 ped/1166
MeSH	D002925

**Primary ciliary dyskinesia (PCD)**, also known as **immotile ciliary syndrome** or **Kartagener Syndrome (KS)**, is a rare, ciliopathic, autosomal recessive genetic disorder that causes a defect in the action of the cilia lining the respiratory tract (lower and upper, sinuses, Eustachian tube, middle ear) and fallopian tube.

Respiratory epithelial motile cilia, which resemble microscopic "hairs" (although structurally and biologically unrelated to hair), are complex organelles that beat synchronously in the respiratory tract, moving mucus toward the throat. Normally, cilia beat 7 to 22 times per second, and any impairment can result in poor mucociliary clearance, with subsequent upper and lower respiratory infection. Cilia also are involved in other biological processes (such as nitric oxide production), which are currently the

subject of dozens of research efforts. As the functions of cilia become better understood, the understanding of PCD should be expected to advance.

## **Genetics**

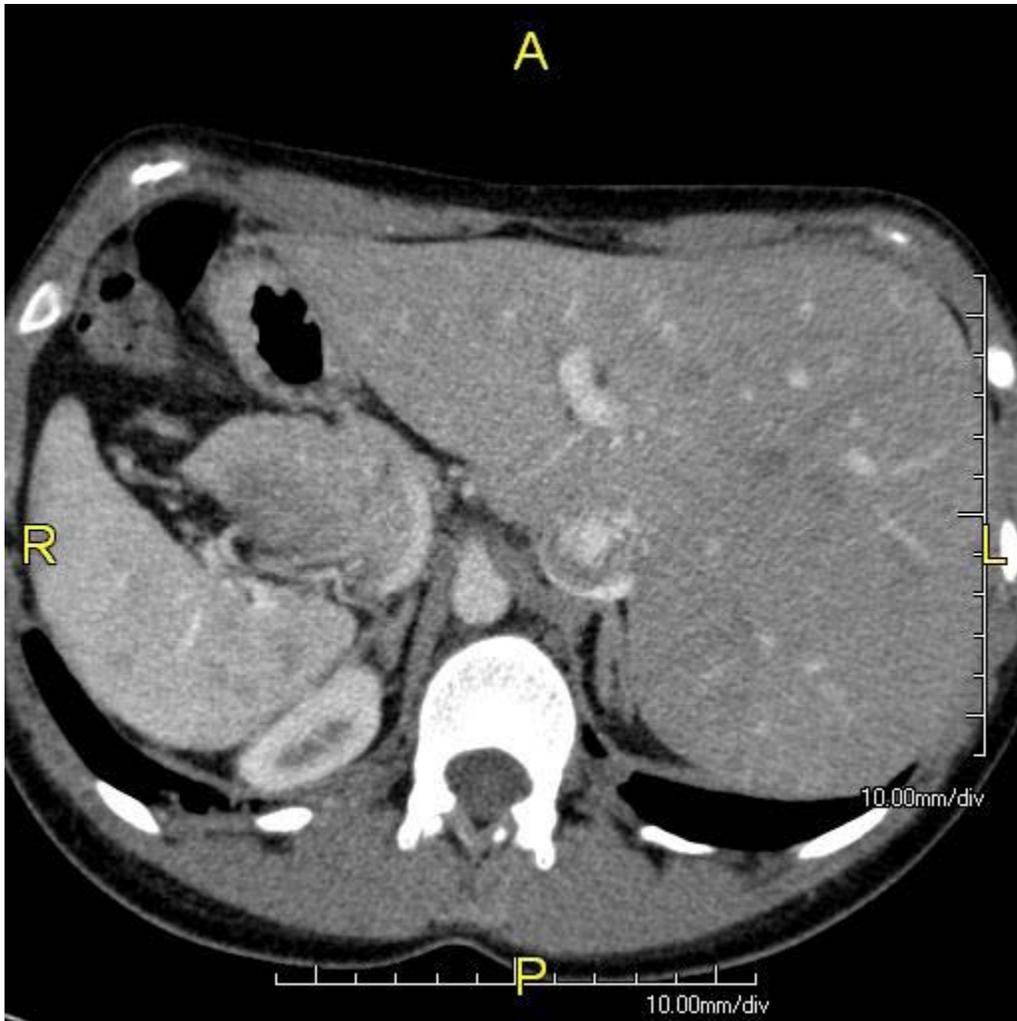
PCD is a genetically heterogeneous disorder affecting motile cilia which are made up of approximately 250 proteins. Around 90% of individuals with PCD have ultrastructural defects affecting protein(s) in the outer and/or inner dynein arms which give cilia their motility, with roughly 38% of these defects caused by mutations on two genes, DNAI1 and DNAH5, both of which code for proteins found in the ciliary outer dynein arm.

There is an international effort to identify genes that code for inner dynein arm proteins or proteins from other ciliary structures (radial spokes, central apparatus, etc.) associated with PCD. The role of DNAH5 in heterotaxy syndromes and left-right asymmetry is also under investigation.

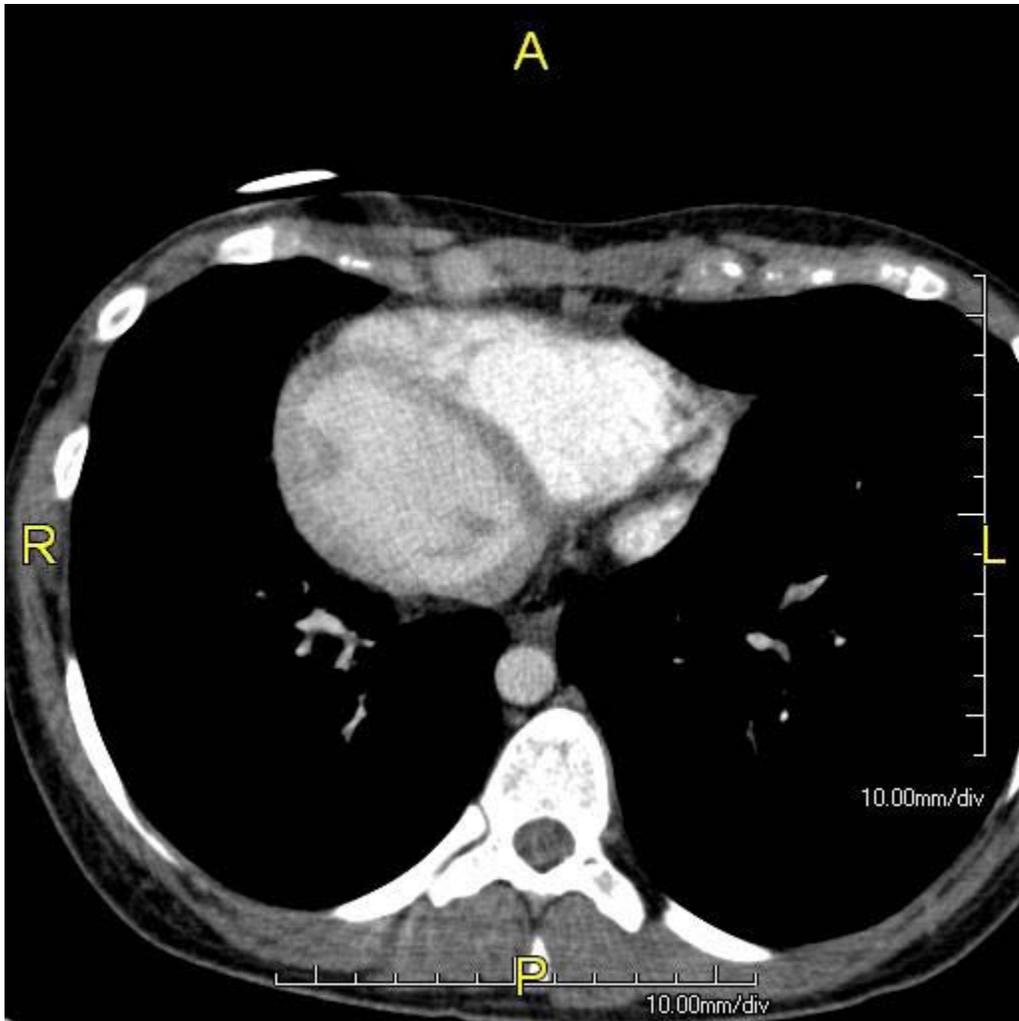
<b>Type</b>	<b>OMIM</b>	<b>Gene</b>	<b>Locus</b>
CILD1	244400	DNAI1	9p21-p13
CILD2	606763	?	19q13.3-qter
CILD3	608644	DNAH5	5p
CILD4	608646	?	15q13
CILD5	608647	?	16p12
CILD6	610852	TXNDC3	7p14-p13
CILD7	611884	DNAH11	7p21
CILD8	612274	?	15q24-q25
CILD9	612444	DNAI2	17q25
CILD10	612518	KTU	14q21.3
CILD11	612649	RSPH4A	6q22
CILD12	612650	RSPH9	6p21
CILD13	613190	LRRC50	16q24.1

## **Classification**

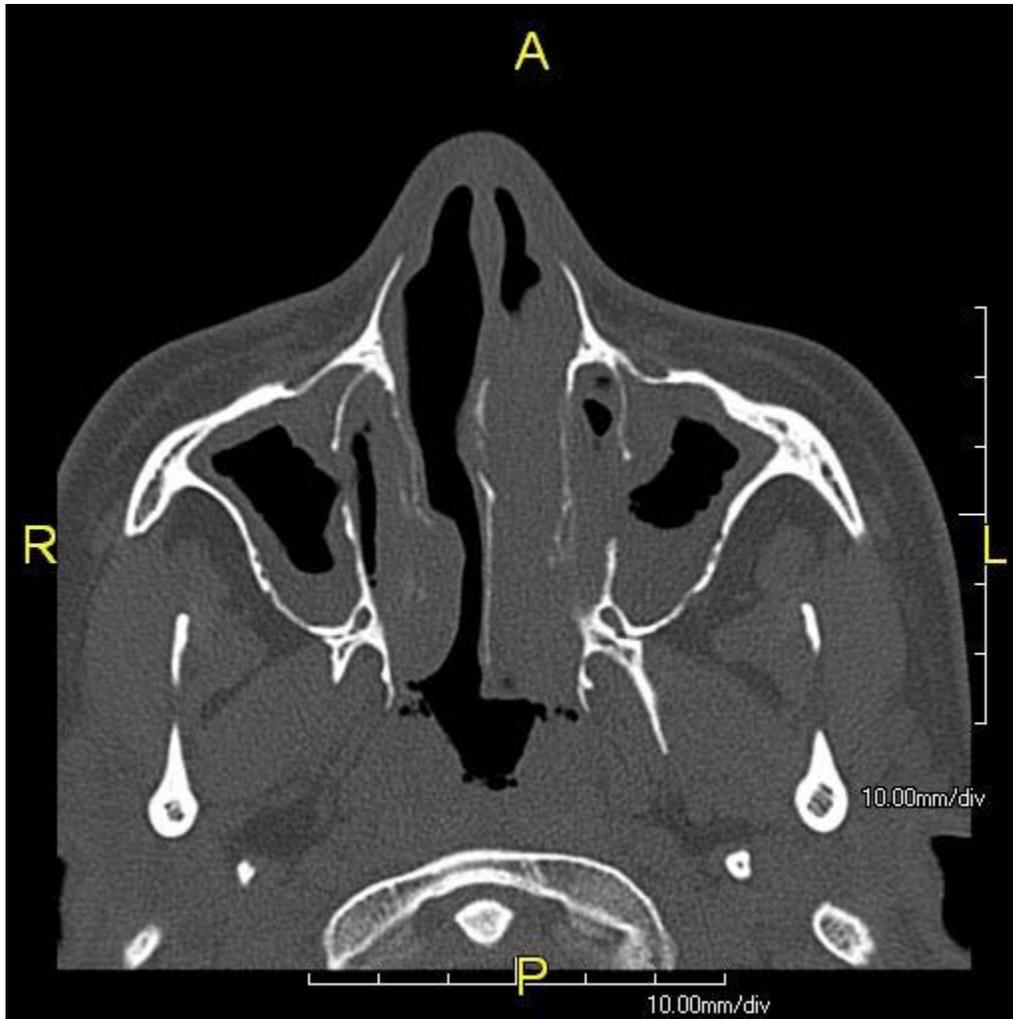
When accompanied by the combination of situs inversus (reversal of the internal organs), chronic sinusitis, and bronchiectasis, it is known as Kartagener syndrome. The phrase "immotile ciliary syndrome" is no longer favored as the cilia does have movement, but may be inefficient or unsynchronized.



Axial CT image showing situs inversus. The slice is seen from below, with the liver and IVC on the left and the spleen and aorta on the right.



Axial CT image showing dextrocardia with the IVC and morphologic right ventricle on the left and the left ventricle on the right



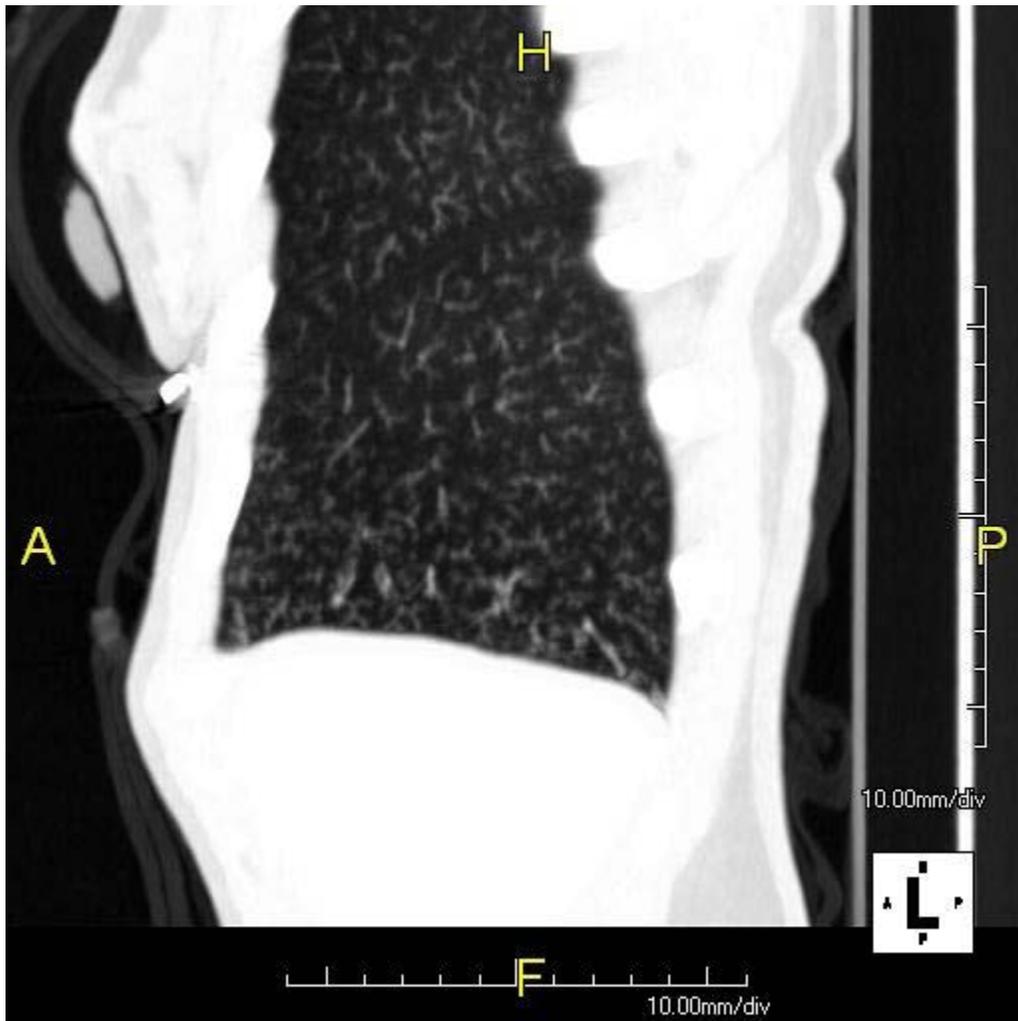
Axial CT image showing chronic sinusitis in an individual with Kartagener syndrome

### ***Signs and symptoms***

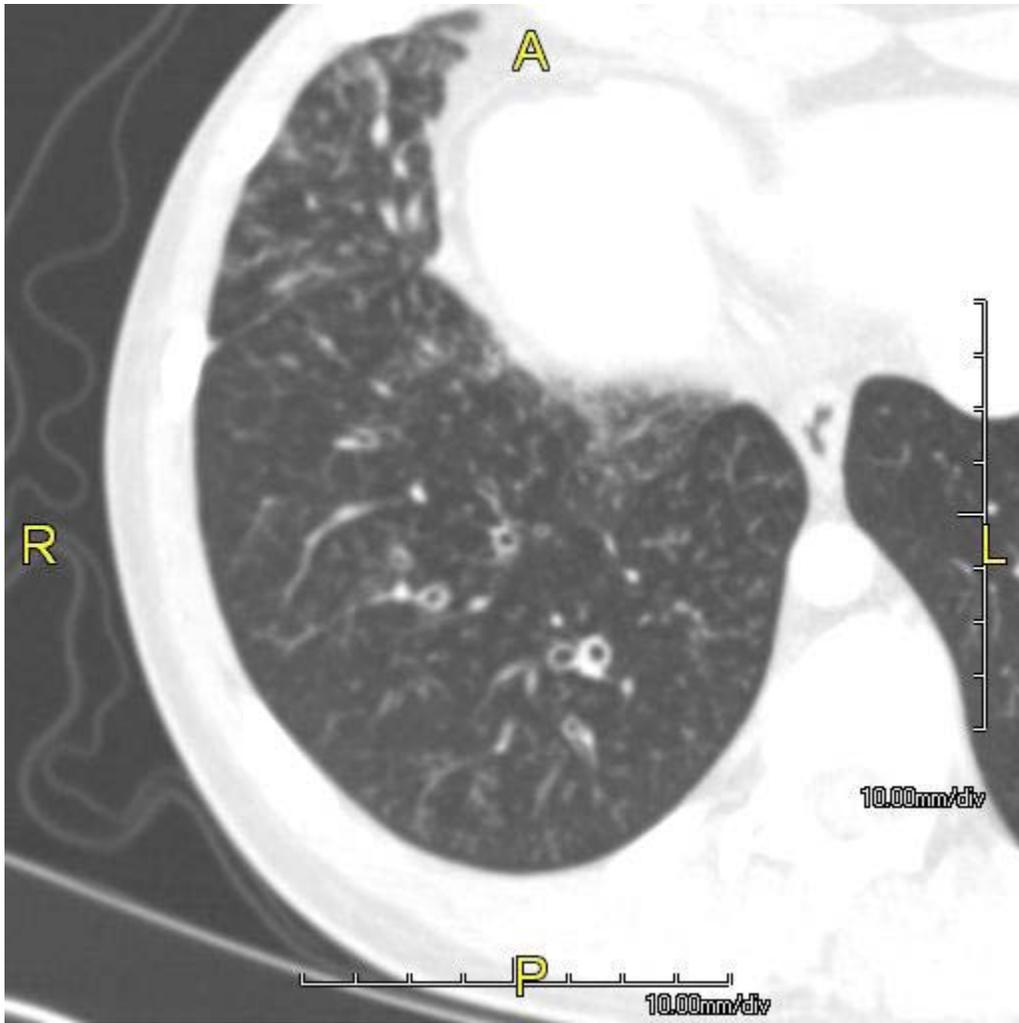
The main consequence of impaired ciliary function is reduced or absent mucus clearance from the lungs, and susceptibility to chronic recurrent respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media. Progressive damage to the respiratory system is common, including progressive bronchiectasis beginning in early childhood, and sinus disease (sometimes becoming severe in adults). However, diagnosis is often missed early in life despite the characteristic signs and symptoms.

Many affected individuals experience hearing loss and show symptoms of glue ear which demonstrate variable responsiveness to the insertion of myringotomy tubes or grommets. Some patients have been having a poor sense of smell, which is believed to accompany high mucus production in the sinuses (although others report normal - or even acute - sensitivity to smell and taste). Clinical progression of the disease is variable with lung transplantation required in severe cases. Susceptibility to infections can be drastically reduced by an early diagnosis. Treatment with various chest physiotherapy techniques

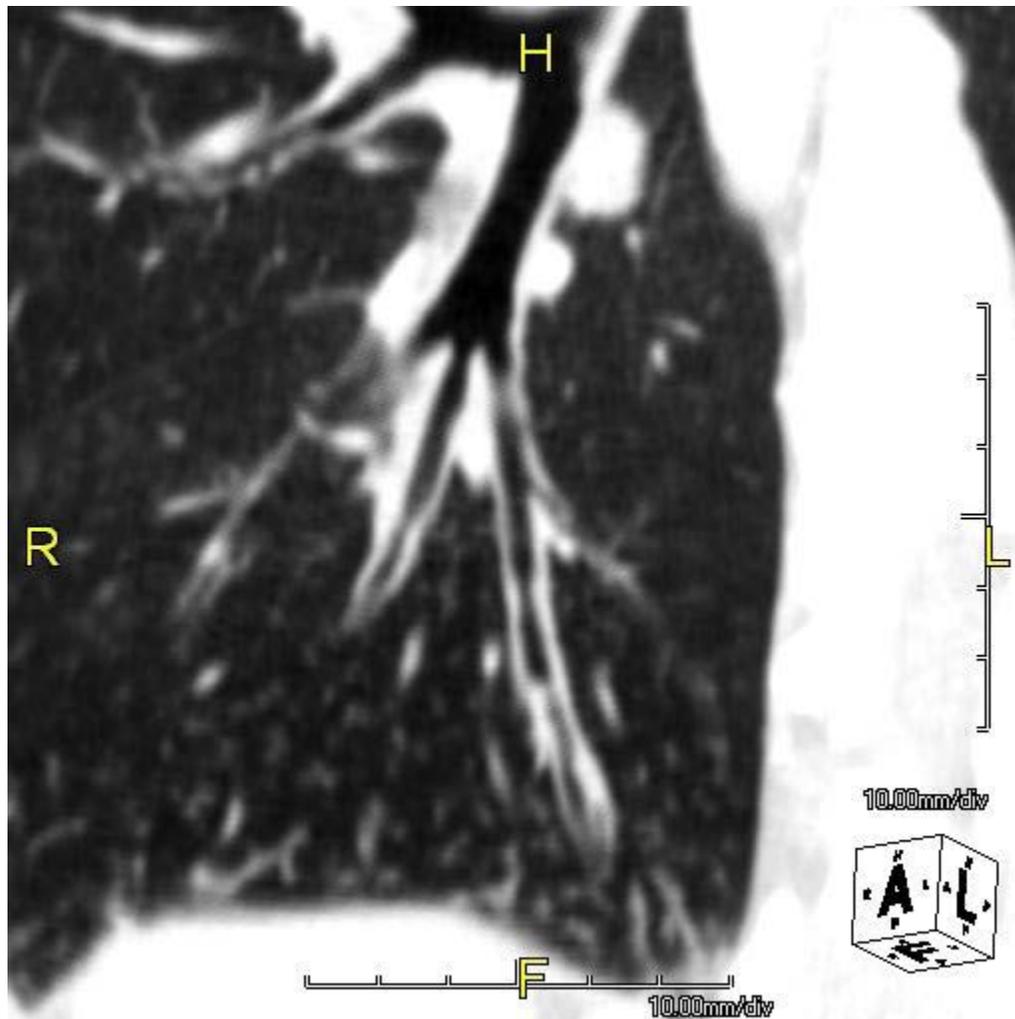
has been observed to reduce the incidence of lung infection and to slow the progression of bronchiectasis dramatically. Aggressive treatment of sinus disease beginning at an early age is believed to slow long-term sinus damage (although this has not yet been adequately documented). Aggressive measures to enhance clearance of mucus, prevent respiratory infections, and treat bacterial superinfections have been observed to slow lung-disease progression. Although the true incidence of the disease is unknown, it is estimated to be 1 in 32,000, although the actual incidence may be as high as 1 in 15,000.



Sagittal CT image showing "tree in bud" appearance of mucous impaction in distal small airways related to primary ciliary dyskinesia



CT image showing dilated and thickened medium sized airways (bronchiectasis) in a patient with Kartagener syndrome



Oblique sagittal CT image showing lower lobe cylindrical bronchiectasis in the same patient

### ***Pathophysiology***

This disease is genetically inherited. Structures that make up the cilia including inner and/or outer dynein arms, central apparatus, radial spokes, etc. are missing or dysfunctional and thus the axoneme structure lacks the ability to move. Axonemes are the elongated structures that make up cilia and flagella. Additionally, there may be chemical defects that interfere with ciliary function in the presence of adequate structure. Whatever the underlying cause, dysfunction of the cilia begins during and impacts the embryologic phase of development.

Specialised monocilia are at the heart of this problem. They lack the central-pair microtubules of ordinary motile cilia and so rotate clockwise rather than beat; in Hensen's node at the anterior end of the primitive streak in the embryo, these are angled posteriorly such that they prescribe a D-shape rather than a circle. This has been shown to generate a

net leftward flow in mouse and chick embryos, and sweeps the Sonic Hedgehog (*Shh*) protein to the left, triggering normal asymmetrical development.

However, in some individuals with PCD, mutations thought to be in the gene coding for the key structural protein left-right dynein (*Ird*) result in monocilia which do not rotate. There is therefore no flow generated in the node, *Shh* moves at random within it, and 50% of those affected develop situs inversus which can occur with or without dextrocardia, where the laterality of the internal organs is the mirror-image of normal. Affected individuals therefore have Kartagener syndrome. This is not the case with some PCD-related genetic mutations: at least 6% of the PCD population have a condition called situs ambiguus or heterotaxy where organ placement or development is neither typical (situs solitus) nor totally reversed (situs inversus totalis) but is a hybrid of the two. Splenic abnormalities such as polysplenia, asplenia and complex congenital heart defects are more common in individuals with situs ambiguus and PCD, as they are in all individuals with situs ambiguus.

The genetic forces linking failure of nodal monocilia and situs issues and the relationship of those forces to PCD are the subject of intense research interest. For now hypotheses abound—some, like the one above, are generally accepted. However, knowledge in this area is constantly advancing.

### **Relation to other rare genetic disorders**

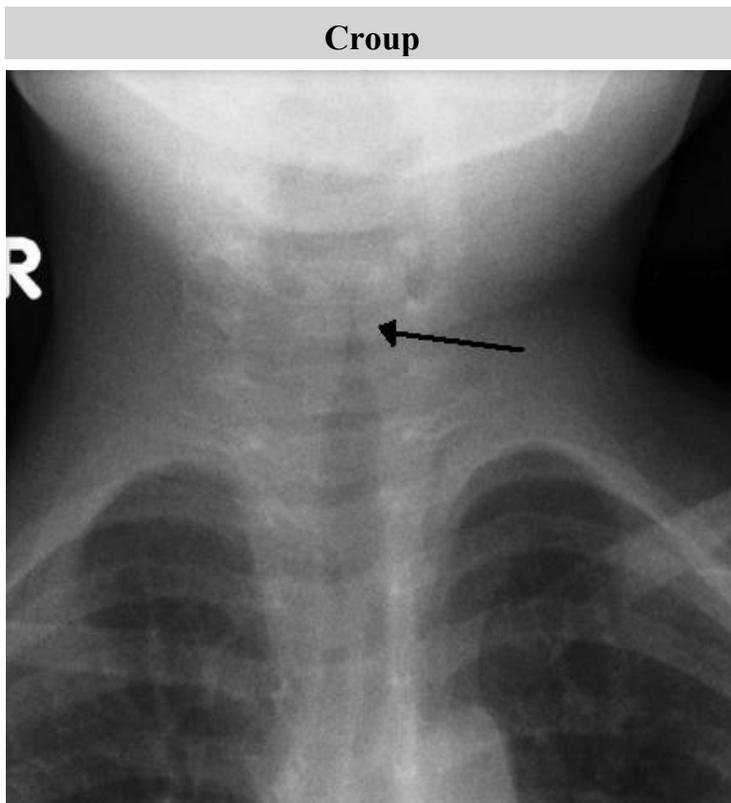
Recent findings in genetic research have suggested that a large number of genetic disorders, both genetic syndromes and genetic diseases, that were not previously identified in the medical literature as related, may be, in fact, highly related in the genotypical root cause of the widely-varying, phenotypically-observed disorders. Thus, PCD is a ciliopathy. Other known ciliopathies include Bardet-Biedl syndrome, polycystic kidney and liver disease, nephronophthisis, Alstrom syndrome, Meckel-Gruber syndrome and some forms of retinal degeneration.

### **History**

The classic symptom combination associated with PCD was first described by A. K. Zivert in 1904, while Kartagener published his first report on the subject in 1933.

## Chapter 7

# Croup



The steeple sign as seen on an AP neck X-ray of a child with croup

<b>ICD-10</b>	J05.0
<b>ICD-9</b>	464.4
<b>DiseasesDB</b>	13233
<b>MedlinePlus</b>	000959
<b>eMedicine</b>	ped/510 emerg/370 radio/199
<b>MeSH</b>	D003440

**Croup** (or **laryngotracheobronchitis**) is a respiratory condition that is usually triggered by an acute viral infection of the upper airway. The infection leads to swelling inside the throat, which interferes with normal breathing and produces the classical symptoms of a "barking" cough, stridor, and hoarseness. It may produce mild, moderate, or severe symptoms, which often worsen at night. It is often treated with a single dose of oral steroids; occasionally epinephrine is used in more severe cases. Hospitalization is rarely required.

Croup is diagnosed on clinical grounds once potentially more severe causes of symptoms have been excluded (i.e. epiglottitis or an airway foreign body). Further investigations—such as blood tests, X-rays, and cultures—are usually not needed. It is a relatively common condition that affects about 15% of children at some point, most commonly between 6 months and 5–6 years of age. It is almost never seen in teenagers or adults.

Once due primarily to diphtheria, this cause is now primarily of historical significance in the Western world due to the success of vaccination.

### ***Signs and symptoms***

Croup is characterized by a "barking" cough, stridor, hoarseness, and difficult breathing which usually worsens at night. The "barking" cough is often described as resembling the call of a seal or sea lion. The stridor is worsened by agitation or crying, and if it can be heard at rest, it may indicate critical narrowing of the airways. As croup worsens, stridor may decrease considerably.

Other symptoms include fever, coryza (symptoms typical of the common cold), and chest wall indrawing. Drooling or a very sick appearance indicate other medical conditions.

### ***Causes***

Croup is usually deemed to be due to a viral infection. Others use the term more broadly, to include acute laryngotracheitis, spasmodic croup, laryngeal diphtheria, bacterial tracheitis, laryngotracheobronchitis, and laryngotracheobronchopneumonitis. The first two conditions involve a viral infection and are generally milder with respect to symptomatology; the last four are due to bacterial infection and are usually of greater severity.

### ***Viral***

Viral croup/acute laryngotracheitis caused by parainfluenza virus, primarily types 1 and 2, in 75% of cases. Other viral etiologies include influenza A and B, measles, adenovirus and respiratory syncytial virus (RSV). Spasmodic croup is caused by the same group of viruses as acute laryngotracheitis, but lacks the usual signs of infection (such as fever, sore throat, and increased white blood cell count). Treatment, and response to treatment, are also similar.

## Bacterial

Bacterial croup may be divided into laryngeal diphtheria, bacterial tracheitis, laryngotracheobronchitis, and laryngotracheobronchopneumonitis. Laryngeal diphtheria is due to *Corynebacterium diphtheriae* while bacterial tracheitis, laryngotracheobronchitis, and laryngotracheobronchopneumonitis are usually due to a primary viral infection with secondary bacterial growth. The most common bacteria implicated are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis*.

## Pathophysiology

The viral infection that causes croup leads to swelling of the larynx, trachea, and large bronchi due to infiltration of white blood cells (especially histiocytes, lymphocytes, plasma cells, and neutrophils). Swelling produces airway obstruction which, when significant, leads to dramatically increased work of breathing and the characteristic turbulent, noisy airflow known as stridor.

## Diagnosis

Feature	The Westley Score: Classification of croup severity					
	Number of points assigned for this feature					
	0	1	2	3	4	5
Chest wall retraction	None	Mild	Moderate	Severe		
Stridor	None	With agitation	At rest			
Cyanosis	None				With agitation	At rest
Level of consciousness	Normal					Disoriented
Air entry	Normal	Decreased	Markedly decreased			

Croup is a clinical diagnosis. The first step is to exclude other obstructive conditions of the upper airway, especially epiglottitis, an airway foreign body, subglottic stenosis, angioedema, retropharyngeal abscess, and bacterial tracheitis.

A frontal X-ray of the neck is not routinely performed, but if it is done, it may show a characteristic narrowing of the trachea, called the steeple sign. The steeple sign is suggestive of the diagnosis, but is absent in half of cases.

Other investigations (such as blood tests and viral culture) are discouraged as they may cause unnecessary agitation and thus worsen the stress on the compromised airway. While viral cultures, obtained via nasopharyngeal aspiration, can be used to confirm the

exact cause, these are usually restricted to research settings. Bacterial infection should be considered if a person does not improve with standard treatment, at which point further investigations may be indicated.

## Severity

The most commonly used system for classifying the severity of croup is the Westley score. It is primarily used for research purposes rather than in clinical practice. It is the sum of points assigned for five factors: level of consciousness, cyanosis, stridor, air entry, and retractions. The points given for each factor is listed in the table to the right, and the final score ranges from 0 to 17.

- A total score of  $\leq 2$  indicates *mild* croup. The characteristic barking cough and hoarseness may be present, but there is no stridor at rest.
- A total score of 3–5 is classified as *moderate* croup. It presents with easily heard stridor, but with few other signs.
- A total score of 6–11 is *severe* croup. It also presents with obvious stridor, but also features marked chest wall indrawing.
- A total score of  $\geq 12$  indicates impending respiratory failure. The barking cough and stridor may no longer be prominent at this stage.

85% of children presenting to the emergency department have mild disease; severe croup is rare (<1%).

## Prevention

Many cases of croup have been prevented by immunization for influenza and diphtheria. At one time, croup referred to a diphtherial disease, but with vaccination, diphtheria is now rare in the developed world.

## Treatment

Children with croup are generally kept as calm as possible. Steroids are given routinely, with epinephrine used in severe cases. Children with oxygen saturations under 92% should receive oxygen, and those with severe croup may be hospitalized for observation. If oxygen is needed, "blow-by" administration (holding an oxygen source near the child's face) is recommended, as it causes less agitation than use of a mask. With treatment, less than 0.2% of people require endotracheal intubation.

## Steroids

Corticosteroids, such as dexamethasone and budesonide, have been shown to improve outcomes in children with all severities of croup. However, significant relief is often not obtained for up to six hours after administration, and lasts for only about 12 hours. While effective when given orally, parenterally, or by inhalation, the oral route is preferred. A

single dose is usually all that is required, and is generally considered to be quite safe. Dexamethasone at doses of 0.15, 0.3 and 0.6 mg/kg appear to be all equally effective.

## **Epinephrine**

Moderate to severe croup may be improved temporarily with nebulized epinephrine. While epinephrine typically produces a reduction in croup severity within 10–30 minutes, the benefits last for only about 2 hours. If the condition remains improved for 2–4 hours after treatment and no other complications arise, the child is typically discharged from the hospital.

## **Other**

While other treatments for croup have been studied, none have sufficient evidence to support their use. Inhalation of hot steam or humidified air is a traditional self-care treatment, but clinical studies have failed to show effectiveness and currently it is rarely used. The use of cough medicines, which usually contain dextromethorphan and/or guaifenesin, are also discouraged. While breathing heliox (a mixture of helium and oxygen) to decrease the work of breathing has been used in the past, there is very little evidence to support its use. Since croup is usually a viral disease, antibiotics are not used unless secondary bacterial infection is suspected. In cases of possible secondary bacterial infection, the antibiotics vancomycin and cefotaxime are recommended. In severe cases associated with influenza A or B, the antiviral neuraminidase inhibitors may be administered.

## **Prognosis**

Viral croup is usually a self-limited disease, but can very rarely result in death from respiratory failure and/or cardiac arrest. Symptoms usually improve within two days, but may last for up to seven days. Other uncommon complications include bacterial tracheitis, pneumonia, and pulmonary edema.

## **Epidemiology**

Croup affects about 15% of children, and usually presents between the ages of 6 months and 5–6 years. It accounts for about 5% of hospital admissions in this population. In rare cases, it may occur in children as young as 3 months and as old as 15 years. Males are affected 50% more frequently than are females, and there is an increased prevalence in autumn (fall).

## **History**

The word *croup* comes from the Early Modern English verb *croup*, meaning "to cry hoarsely"; the name was first applied to the disease in Scotland and popularized in the 18th century. Diphtheritic croup has been known since the time of Homer's Ancient Greece and it was not until 1826 that viral croup was differentiated from croup due to

diphtheria by Bretonneau. Viral croup was thus called "faux-croup" by the French, as "croup" then referred to a disease caused by the diphtheria bacteria. Croup due to diphtheria has become nearly unknown due to the advent of effective immunization.

## Chapter 8

# Eosinophilic Pneumonia

### Eosinophilic pneumonia

<b>ICD-10</b>	J82.
<b>ICD-9</b>	518.3
<b>MedlinePlus</b>	000105
<b>MeSH</b>	D011657

**Eosinophilic pneumonia (EP)** is a disease in which a certain type of white blood cell called an eosinophil accumulates in the lung. These cells cause disruption of the normal air spaces (alveoli) where oxygen is extracted from the atmosphere. Several different kinds of eosinophilic pneumonia exist and can occur in any age group. The most common symptoms include cough, fever, difficulty breathing, and sweating at night. EP is diagnosed by a combination of characteristic symptoms, findings on a physical examination by a health provider, and the results of blood tests and x-rays. Prognosis is excellent once most EP is recognized and treatment with corticosteroids is begun.

### ***Types of eosinophilic pneumonia***

Eosinophilic pneumonia is divided into different categories depending upon whether a cause can be determined or not. Known causes include certain medications or environmental triggers, parasitic infections, and cancer. EP can also occur when the immune system attacks the lungs, a disease called Churg-Strauss syndrome. When a cause can not be found, the EP is labeled "idiopathic." Idiopathic EP can be divided into "acute eosinophilic pneumonia" (AEP) and "chronic eosinophilic pneumonia" (CEP) depending on the symptoms a person is experiencing.

### ***Symptoms***

Most causes of eosinophilic pneumonia have similar symptoms. Cough, fever, increasing breathlessness, and night sweats are prominent and almost universal. Acute eosinophilic pneumonia typically follows a rapid course. Fever and cough may develop only one or two weeks before difficulties breathing progress to the point of respiratory failure

requiring mechanical ventilation. Chronic eosinophilic pneumonia usually follows a slower course. Symptoms accumulate over several months and include fevers, cough, breathlessness, wheezing, and weight loss. Individuals with CEP are often diagnosed with asthma before CEP is finally recognized.

EP due to medications or environmental exposures is similar and occurs after an exposure to a known offending agent. EP due to parasitic infections has a similar prodrome in addition to a host of different symptoms related to the variety of underlying parasites. EP in the setting of cancer often develops in the context of a known diagnosis of lung cancer, cervical cancer, etc.

There have been cases of drug-induced eosinophilic pneumonia from daptomycin (Cubicin). Two of these cases have been noted as chronically steroid dependent. (Reference Clinical Infectious Disease 2010:50 (1 March) pp735–739.

### ***Pathophysiology***

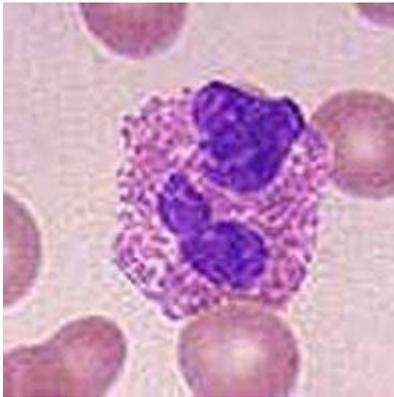


Image of an eosinophil

Eosinophilic pneumonia can develop in several different ways depending on the underlying cause of the disease. Eosinophils are thought to play a central role in defending the body against infection by parasites. Many diseases, such as asthma and eczema, are caused when eosinophils overreact to environmental triggers and release an excess of chemicals (cytokines) such as histamine. The common characteristic among different causes of EP is eosinophil overreaction or dysfunction in the lung.

### **Medications and environmental exposures**

Medications, substance abuse, and environmental exposures may all trigger eosinophil dysfunction. Medications such NSAIDs (i.e. ibuprofen), nitrofurantoin, phenytoin, L-tryptophan, daptomycin and ampicillin and drugs of abuse such as inhaled heroin and cocaine may trigger an allergic response which results in EP. Chemicals such as sulfites, aluminum silicate, and cigarette smoke can cause EP when inhaled. A New York City firefighter developed EP after inhalation of dust from the World Trade Center on September 11, 2001.

## **Parasitic infections**

Parasites cause EP in three different ways. Parasites can either invade the lung, live in the lung as part of their life cycle, or be spread to the lung by the bloodstream. Eosinophils migrate to the lung in order to fight the parasites and EP results. Important parasites which invade the lung include *Paragonimus* lung flukes and the tapeworms *Echinococcus* and *Taenia solium*. Important parasites which inhabit the lung as part of their normal life cycle include the worms (helminths) *Ascaris lumbricoides*, *Strongyloides stercoralis* and the hookworms *Ancylostoma duodenale* and *Necator americanus*. When EP is caused by this last group, it is often called "Löffler's syndrome". The final group of parasites cause EP when a large number of eggs are carried into the lungs by the bloodstream. This can include *Trichinella spiralis*, *Strongyloides stercoralis*, *Ascaris lumbricoides*, the hookworms, and the schistosomes.

## **AEP and CEP**

The causes for both AEP and CEP are unknown as of 2005. There is some suspicion that at least AEP is the result of the body's response to some unidentified environmental agent.

## **Diagnosis**

Eosinophilic pneumonia is diagnosed in one of three circumstances: when a complete blood count reveals increased eosinophils and a chest x-ray or computed tomography (CT) identifies abnormalities in the lung, when a biopsy identifies increased eosinophils in lung tissue, or when increased eosinophils are found in fluid obtained by a bronchoscopy (bronchoalveolar lavage (BAL) fluid). Association with medication or cancer is usually apparent after review of a person's medical history. Specific parasitic infections are diagnosed after examining a person's exposure to common parasites and performing laboratory tests to look for likely causes. If no underlying cause is found, a diagnosis of AEP or CEP is made based upon the following criteria. AEP is most likely with respiratory failure after an acute febrile illness of usually less than one week, changes in multiple areas and fluid in the area surrounding the lungs on a chest x-ray, and greater than 25% eosinophils on a BAL. Other typical laboratory abnormalities include an elevated white blood cell count, erythrocyte sedimentation rate, and immunoglobulin E level. Pulmonary function testing usually reveals a restrictive process with reduced diffusion capacity for carbon monoxide. CEP is most likely when the symptoms have been present for more than a month. Laboratory tests typical for CEP include increased blood eosinophils, a high erythrocyte sedimentation rate, iron deficiency anemia, and increased platelets. A chest x-ray can show abnormalities anywhere, but the most specific finding is increased shadow in the periphery of the lung, away from the heart.

## **Treatment**

When eosinophilic pneumonia is related to an illness such as cancer or parasitic infection, treatment of the underlying cause is effective in resolving the lung disease. When due to

AEP or CEP, however, treatment with corticosteroids results in a rapid, dramatic resolution of symptoms over the course of one or two days. Either intravenous methylprednisolone or oral prednisone are most commonly used. In AEP, treatment is usually continued for a month after symptoms disappear and the x-ray returns to normal (usually four weeks total). In CEP, treatment is usually continued for three months after symptoms disappear and the x-ray returns to normal (usually four months total). Inhaled steroids such as fluticasone have been used effectively when discontinuation of oral prednisone has resulted in relapse. Because EP affects the lungs, individuals with EP have difficulty breathing. If enough of the lung is involved, it may not be possible for a person to breathe enough to live without support. Non-invasive machines such as a bilevel positive airway pressure machine may be used. Otherwise, placement of a breathing tube into the mouth may be necessary and a ventilator may be used to help the person breathe.

## ***Prognosis***

Eosinophilic pneumonia due to cancer or parasitic infection carries a prognosis related to the underlying illness. AEP and CEP, however, have very little associated mortality as long as intensive care is available and treatment with corticosteroids is given. CEP often relapses when prednisone is discontinued; therefore, some people with CEP require lifelong therapy. Chronic prednisone is associated with many side effects, including increased infections, weakened bones, stomach ulcers, and changes in appearance.

## ***Epidemiology***

Eosinophilic pneumonia is a rare disease. Parasitic causes are most common in geographic areas where each parasite is endemic. AEP can occur at any age, even in previously healthy children, though most patients are between 20 and 40 years of age. Men are affected approximately twice as frequently as women. AEP has been associated with smoking. CEP occurs more frequently in women than men and does not appear to be related to smoking. An association with radiation for breast cancer has been described.

## ***History***

Chronic eosinophilic pneumonia was first described by Carrington in 1969, and it is also known as **Carrington syndrome**. Prior to that, eosinophilic pneumonia was a well described pathologic entity usually associated with medication or parasite exposures. Acute eosinophilic pneumonia was first described in 1989

## Chapter 9

# Hypopnea and Infant Respiratory Distress Syndrome

## Hypopnea

**Hypopnea** (sometimes spelled **hypopnoea**) is a medical term for a disorder which involves episodes of overly shallow breathing or an abnormally low respiratory rate. This differs from apnea in that there remains some flow of air. Hypopnea events may happen while asleep or while awake.

During sleep, hypopnea is classed as a sleep disorder. With moderate to severe hypopnea, sleep is disturbed such that patients may get a full night's sleep but still not feel rested because they did not get the right kind of sleep. The disruption in breathing causes a drop in blood oxygen level, which may in turn disrupt the stages of sleep.

Daytime hypopnea events are mostly limited to those with severely compromised respiratory muscles, as occurs in certain neuromuscular diseases. Similarly, daytime hypopnea can also cause a drop in blood oxygen level.

### ***Etymology***

Hypopnea comes from the Greek roots *hypo-* (meaning *low, under, beneath, down, below normal*) and *pnoe* (meaning *breathing*). Literally it means underbreathing.

### ***General information***

In the context of diagnosis and treatment of sleep disorders, a hypopnea event is not considered to be clinically significant unless there is a 30% (or greater) reduction in flow lasting for 10 seconds or longer and an associated 4% (or greater) desaturation in the person's O<sub>2</sub> levels, or if it results in arousal or fragmentation of sleep.

The direct consequence of hypopnea (as well as apnea) is that the CO<sub>2</sub> in the blood increases and the oxygen level in the patient's blood decrease is proportionate to the severity of the airway obstruction. This disruptive pattern of breathing generates disruptive sleep patterns, the consequences of which being that those individuals may

exhibit increased fatiguability, lethargy, decreased ability to concentrate, increased irritability, and morning headaches. Basically, those individuals are extremely tired due to their inability to get a good night's sleep.

Hypopneas can be either central (i.e., as part of a waxing and waning in breathing effort) or obstructive in origin. During an obstructive hypopnea, in comparison to an obstructive apnea, the airway is only partially closed. However, this closure is still enough to cause a physiological effect (i.e., an oxygen desaturation and/or an increase in breathing effort terminating in arousal).

A hypopnea index (HI) can be calculated by dividing the number of hypopnea events during the sleep period by the number of hours of sleep. The apnea-hypopnea index (AHI) is an index of severity that combines apneas and hypopneas. Combining them both gives an overall severity of sleep apnea including sleep disruptions and desaturations (a low level of oxygen in the blood). The apnea-hypopnea index, like the apnea index and hypopnea index, is calculated by dividing the number of apneas and hypopneas by the number of hours of sleep. Another index that is used to measure sleep apnea is the respiratory disturbance index (RDI). The respiratory disturbance index is similar to the apnea-hypopnea index; however, it also includes respiratory events that do not technically meet the definitions of apneas or hypopneas, but do disrupt sleep.

## **Causes**

Among the causes of hypopnea are:

- anatomical defects such as nasal septum deformation or congenital narrowness of nasal meati and the gullet;
- acute tonsillitis and/or adenoiditis;
- obesity or being overweight;
- neuromuscular disease or any condition that entails weakened respiratory muscles;
- use of sedatives (sleeping pills, etc.);
- alcohol abuse;
- smoking;
- aging;
- others;

most of which are also typical causes of airway obstruction, snoring and sleep apnea.

## **Symptoms**

The most common hypopnea symptom is excessive sleepiness, which results from constant sleep interruption. People with hypopnea often have loud, heavy snoring that is interrupted with choking sounds or loud snorts followed by periods of silence, because not enough air can flow into the lungs through the mouth and nose. The periods of silence

can last 20 seconds or longer and can happen many times each hour, resulting in poor sleep and reduced levels of oxygen in the blood.

Other symptoms of hypopnea may include depression, forgetfulness, mood or behavior changes, trouble concentrating, loss of energy, nervousness, and morning headaches. Not all people with hypopnea experience all of these symptoms and not everyone who has these symptoms has hypopnea.

## ***Consequences***

Hypopnea is a disorder that may result in excessive daytime sleepiness and compromised quality of life, including traffic accidents, diminished productivity in the work place and emotional problems.

Cardiovascular consequences of hypopnea may include myocardial infarction, stroke, psychiatric problems, impotence, cognitive dysfunction, hypertension, coronary heart disease, and memory loss.

## ***Treatment***

The most common treatment for hypopnea is continuous positive airway pressure (CPAP). CPAP is a treatment in which the patient wears a mask over the nose and/or mouth. An air blower forces air through the upper airway. The air pressure is adjusted so that it is just enough to maintain the oxygen saturation levels in the blood. For people with neuromuscular disorders, the most common treatment is the use of BIPAP or other non-invasive ventilation.

Mild hypopnea can often be treated by losing weight or by avoiding sleeping on one's back. Also quitting smoking, and avoiding alcohol, sedatives and hypnotics (soporifics) before sleep can be quite effective.

Surgery is generally a last resort in hypopnea treatment, but is a site-specific option for the upper airway. Depending on the cause of obstruction, surgery may focus on the soft palate, the uvula, tonsils, adenoids or the tongue. There are also more complex surgeries that are performed with the adjustment of other bone structures - the mouth, nose and facial bones.

# Infant respiratory distress syndrome

## Infant respiratory distress syndrome

ICD-10	P22.
ICD-9	769
OMIM	267450
DiseasesDB	6087
MedlinePlus	001563
eMedicine	emerg/15
MeSH	D012127

**Infant respiratory distress syndrome (IRDS)**, also called **neonatal respiratory distress syndrome** or **respiratory distress syndrome of newborn**, previously called **hyaline membrane disease**, is a syndrome in premature infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs. It can also result from a genetic problem with the production of surfactant associated proteins. RDS affects about 1% of newborn infants and is the leading cause of death in preterm infants. The incidence decreases with advancing gestational age, from about 50% in babies born at 26–28 weeks, to about 25% at 30–31 weeks. The syndrome is more frequent in infants of diabetic mothers and in the second born of premature twins.

IRDS is distinct from pulmonary hypoplasia, another leading cause of neonatal death that involves respiratory distress.

### ***Clinical course***

Respiratory distress syndrome begins shortly after birth and is manifest by tachypnea, tachycardia, chest wall retractions (recession), expiratory grunting, flaring of the nostrils and cyanosis during breathing efforts.

As the disease progresses, the baby may develop ventilatory failure (rising carbon dioxide concentrations in the blood), and prolonged cessations of breathing ("apnea"). Whether treated or not, the clinical course for the acute disease lasts about 2 to 3 days. During the first, the patient worsens and requires more support. During the second the baby may be remarkably stable on adequate support and resolution is noted during the third day, heralded by a prompt diuresis. Despite huge advances in care, RDS remains the most common single cause of death in the first month of life of the developed world. Complications include metabolic disorders (acidosis, low blood sugar), patent ductus arteriosus, low blood pressure, chronic lung changes, and intracranial hemorrhage. The

disease is frequently complicated by prematurity and its additional defects in other organ function.

### ***Histopathology***

The characteristic histopathology seen in babies who die from RDS was the source of the name "hyaline membrane disease". These waxy-appearing layers line the collapsed tiny air sacs ("alveoli") of the lung. In addition, the lungs show bleeding, over-distention of airways and damage to the lining cells.

### ***Pathophysiology***

The lungs of infants with respiratory distress syndrome are developmentally deficient in a material called surfactant, which helps prevent collapse of the terminal air-spaces (the future site of alveolar development) throughout the normal cycle of inhalation and exhalation. Surfactant is a complex system of lipids, proteins and glycoproteins which are produced in specialized lung cells called Type II cells or Type II pneumocytes. The surfactant is packaged by the cell in structures called lamellar bodies, and extruded into the air-spaces. The lamellar bodies then unfold into a complex lining of the air-space. This layer reduces the surface tension of the fluid that lines the air-space. Surface tension is responsible for approximately 2/3 of the elastic recoil forces. In the same way that a bubble will contract to give the smallest surface area for a given volume, so the air/water interface means that the liquid surface will tend towards being as small as possible, thereby causing the air-space to contract. By reducing surface tension, surfactant prevents the air-spaces from completely collapsing on exhalation. In addition, the decreased surface tension allows re-opening of the air-space with a lower amount of force. Therefore, without adequate amounts of surfactant, the air-spaces collapse and are very difficult to expand. Microscopically, a surfactant deficient lung is characterized by collapsed air-spaces alternating with hyper-expanded areas, vascular congestion and, in time, hyaline membranes. Hyaline membranes are composed of fibrin, cellular debris, red blood cells, rare neutrophils and macrophages. They appear as an eosinophilic, amorphous material, lining or filling the air spaces and blocking gas exchange. As a result, blood passing through the lungs is unable to pick up oxygen and unload carbon dioxide. Blood oxygen levels fall and carbon dioxide rises, resulting in rising blood acid levels and hypoxia. Structural immaturity, as manifest by decreased number of gas-exchange units and thicker walls, also contributes to the disease process. Therapeutic oxygen and positive-pressure ventilation, while potentially life-saving, can also damage the lung. The diagnosis is made by the clinical picture and the chest xray, which demonstrates decreased lung volumes (bell-shaped chest), absence of the thymus (after about 6 hours), a small (0.5–1 mm), discrete, uniform infiltrate (sometimes described as a "ground glass" appearance) that involves all lobes of the lung, and air-bronchograms (i.e. the infiltrate will outline the larger airways passages which remain air-filled). In severe cases, this becomes exaggerated until the cardiac borders become inapparent (a 'white-out' appearance).

## ***Prevention***

Most cases of infant respiratory distress syndrome can be ameliorated or prevented if mothers who are about to deliver prematurely can be given glucocorticoids, one group of hormones. This speeds the production of surfactant. For very premature deliveries, a glucocorticoid is given without testing the fetal lung maturity. The American College of Obstetricians and Gynecologists (ACOG), Royal College of Medicine, and other major organizations have recommended antenatal glucocorticoid treatment for women at risk for preterm delivery prior to 34 weeks of gestation. In pregnancies of greater than 30 weeks, the fetal lung maturity may be tested by sampling the amount of surfactant in the amniotic fluid, obtained by inserting a needle through the mother's abdomen and uterus. Several tests are available that correlate with the production of surfactant. These include the lecithin-sphingomyelin ratio ("L/S ratio"), the presence of phosphatidol glycerol (PG), and more recently, the surfactant/albumin (S/A) ratio. For the L/S ratio, if the result is less than 2:1, the fetal lungs may be surfactant deficient. The presence of PG usually indicates fetal lung maturity. For the S/A ratio, the result is given as mg of surfactant per gm of protein. An S/A ratio <35 indicates immature lungs, between 35-55 is indeterminate, and >55 indicates mature surfactant production (correlates with an L/S ratio of 2.2 or greater).

## ***Treatment***

Oxygen is given with a small amount of continuous positive airway pressure ("CPAP"), and intravenous fluids are administered to stabilize the blood sugar, blood salts, and blood pressure. If the baby's condition worsens, an endotracheal tube (breathing tube) is inserted into the trachea and intermittent breaths are given by a mechanical device. An exogenous preparation of surfactant, either synthetic or extracted from animal lungs, is given through the breathing tube into the lungs. One of the most commonly used surfactants is Survanta, derived from cow lungs, which can decrease the risk of death in hospitalized very-low-birth-weight infants by 30%. Such small premature infants may remain ventilated for months. A line of research shows that an aerosol of perfluorocarbon can reduce inflammation in piglets. Chronic lung disease including bronchopulmonary dysplasia are common in severe RDS. The etiology of BPD is problematic and may be due to oxygen, overventilation or underventilation. The mortality rate for babies greater than 27 weeks gestation is less than 10%.

Extracorporeal membrane oxygenation (ECMO) is a potential treatment, providing oxygenation through an apparatus that imitates the gas exchange process of the lungs. However, newborns cannot be placed on ECMO if they are under 4.5 pounds (2 kg), because they have extremely small vessels for cannulation, thus hindering adequate flow because of limitations from cannula size and subsequent higher resistance to blood flow (compare with vascular resistance). Furthermore, in infants aged less than 34 weeks of gestation several physiologic systems are not well-developed, specially the cerebral vasculature and germinal matrix, resulting in high sensitivity to slight changes in pH, PaO<sub>2</sub>, and intracranial pressure. Subsequently, preterm infants are at unacceptably high risk for intraventricular hemorrhage (IVH) if administered ECMO at a gestational age

less than 32 weeks. Also later, given the risk of IVH, it has become standard practice to ultrasound the brain prior to administering ECMO. Therefore, the device cannot be used for most premature newborns.

### ***Related disorders***

Acute respiratory distress syndrome (ARDS) has some similarities to IRDS.

### ***Famous victims***

- In 1963, Patrick Bouvier Kennedy, son of President John F. Kennedy and First Lady Jacqueline Kennedy, died of RDS two days after his premature birth at 34 weeks gestation.
- In 1992, Freddie Highmore survived RDS after being born at 29 weeks gestation.

## Chapter 10

# Lung Transplantation

**Lung transplantation**, or **pulmonary transplantation** is a surgical procedure in which a patient's diseased lungs are partially or totally replaced by lungs which come from a donor. While lung transplants carry certain associated risks, they can also extend life expectancy and enhance the quality of life for end-stage pulmonary patients.

### ***Qualifying conditions***

Lung transplantation is the therapeutic measure of last resort for patients with end-stage lung disease who have exhausted all other available treatments without improvement. A variety of conditions may make such surgery necessary. As of 2005, the most common reasons for lung transplantation in the United States were:

- 27% chronic obstructive pulmonary disease (COPD), including emphysema;
- 16% idiopathic pulmonary fibrosis;
- 14% cystic fibrosis;
- 12% idiopathic (formerly known as "primary") pulmonary hypertension;
- 5% alpha 1-antitrypsin deficiency;
- 2% replacing previously transplanted lungs that have since failed;
- 24% other causes, including bronchiectasis and sarcoidosis.

### ***Contraindications***

Despite the severity of a patient's respiratory condition, certain preexisting conditions may make a person a poor candidate for lung transplantation. These conditions include:

- concurrent chronic illness (e.g. congestive heart failure, kidney disease, liver disease);
- current infections, including HIV and hepatitis, although more and more often Hepatitis C patients are both being transplanted and are also being used as donors if the recipient is Hepatitis C positive.
- current or recent cancer;
- current use of alcohol, tobacco, or illegal drugs;
- age;
- psychiatric conditions;
- history of noncompliance with medical instructions.

## ***History***

The history of organ transplants began with several attempts that were unsuccessful due to transplant rejection. Animal experimentation by various pioneers, including Vladimir Demikhov and Dominique Metras, during the 1940s and 1950s, first demonstrated that the procedure was technically feasible. James Hardy of the University of Mississippi performed the first human lung transplant in 1963. Following a left lung transplantation, the patient survived for 18 days. From 1963-1978, multiple attempts at lung transplantation failed because of rejection and problems with anastomotic bronchial healing. It was only after the invention of the heart-lung machine, coupled with the development of immunosuppressive drugs such as cyclosporine, that organs such as the lungs could be transplanted with a reasonable chance of patient recovery.

The first successful transplant surgery involving the lungs was a heart-lung transplant, performed by Dr. Bruce Reitz of Stanford University on a woman who had idiopathic pulmonary hypertension.

- 1983: First successful single lung transplant (Tom Hall) by Joel Cooper (Toronto)
- 1986: First successful double lung transplant (Ann Harrison) by Joel Cooper (Toronto)
- 1988: First successful double lung transplant for cystic fibrosis by Joel Cooper (Toronto)

## ***Transplant requirements***

### **Requirements for potential donors**

There are certain requirements for potential lung donors, due to the needs of the potential recipient. In the case of living donors, this is also in consideration of how the surgery will affect the donor.

- healthy;
- size match; the donated lung or lungs must be large enough to adequately oxygenate the patient, but small enough to fit within the recipient's chest cavity;
- age;
- blood type.

### **Requirements for potential recipients**

While each transplant center is free to set its own criteria for transplant candidates, certain requirements are generally agreed upon:

- end-stage lung disease;
- has exhausted other available therapies without success;
- no other chronic medical conditions (e.g. heart, kidney, liver);

- no current infections or recent cancer. There are certain cases where preexisting infection is unavoidable, as with many patients with cystic fibrosis. In such cases, transplant centers, at their own discretion, may accept or reject patients with current infections of *B. cepacia* or *MRSA*.
- no HIV or hepatitis;
- no alcohol, smoking, or drug abuse;
- within an acceptable weight range (marked undernourishment or obesity are both associated with increased mortality);
- age (single vs. double tx);
- acceptable psychological profile;
- has social support system;
- financially able to pay for expenses; (in places where medical care is paid for directly by the patient)
- able to comply with post-transplant regimen. A lung transplant is a major operation, and following the transplant, the patient must be willing to adhere to a lifetime regimen of medications as well as continuing medical care.

### **Medical tests for potential transplant candidates**

Patients who are being considered for placement on the organ transplant list must undergo an extensive series of medical tests in order to evaluate their overall health status and suitability for transplant surgery.

- blood typing; the blood type of the recipient must match that of the donor due to certain antigens that are present on donated lungs. A mismatch of blood type can lead to a strong response by the immune system and subsequent rejection of the transplanted organs;
- tissue typing; ideally, the lung tissue would also match as closely as possible between the donor and the recipient, but the desire to find a highly compatible donor organ must be balanced against the patient's immediacy of need;
- Chest X-ray - PA & LAT, to verify the size of the lungs and the chest cavity;
- pulmonary function tests;
- CT Scan (High Resolution Thoracic & Abdominal);
- Bone mineral density scan;
- MUGA (Gated cardiac blood pool scan);
- Cardiac stress test (Dobutamine/Thallium scan);
- ventilation/perfusion (V/Q) scan;
- electrocardiogram;
- cardiac catheterization;
- echocardiogram.

### **Lung allocation score**

Prior to 2005, donor lungs within the United States were allocated by the United Network for Organ Sharing on a first-come, first-serve basis to patients on the transplant list. This was replaced by the current system, in which prospective lung recipients of age of 12 and

older are assigned a lung allocation score or LAS, which takes into account various measures of the patient's health. The new system allocates donated lungs according to the immediacy of need rather than how long a patient has been on the transplant list. Patients who are under the age of 12 are still given priority based on how long they have been on the transplant waitlist. The length of time spent on the list is also the deciding factor when multiple patients have the same lung allocation score.

Patients who are accepted as good potential transplant candidates must carry a pager with them at all times in case a donor organ becomes available. These patients must also be prepared to move to their chosen transplant center at a moment's notice. Such patients may be encouraged to limit their travel within a certain geographical region in order to facilitate rapid transport to a transplant center.

## ***Types of lung transplant***

### **Lobe**

A lobe transplant is a surgery in which part of a living donor's lung is removed and used to replace part of recipient's diseased lung. This procedure usually involves the donation of lobes from two different people, thus replacing a single lung in the recipient. Donors who have been properly screened should be able to maintain a normal quality of life despite the reduction in lung volume.

### **Single-lung**

Many patients can be helped by the transplantation of a single healthy lung. The donated lung typically comes from a donor who has been pronounced brain-dead.

### **Double-lung**

Certain patients may require both lungs to be replaced. This is especially the case for people with cystic fibrosis, due to the bacterial colonisation commonly found within such patients' lungs; if only one lung were transplanted, bacteria in the native lung could potentially infect the newly transplanted organ.

### **Heart-lung**

Some respiratory patients may also have severe cardiac disease which would necessitate a heart transplant. These patients can be treated by a surgery in which both lungs and the heart are replaced by organs from a donor or donors.

A particularly involved example of this has been termed a "domino transplant" in the media. First performed in 1987, this type of transplant typically involves the transplantation of a heart and lungs into recipient A, whose own healthy heart is removed and transplanted into recipient B.

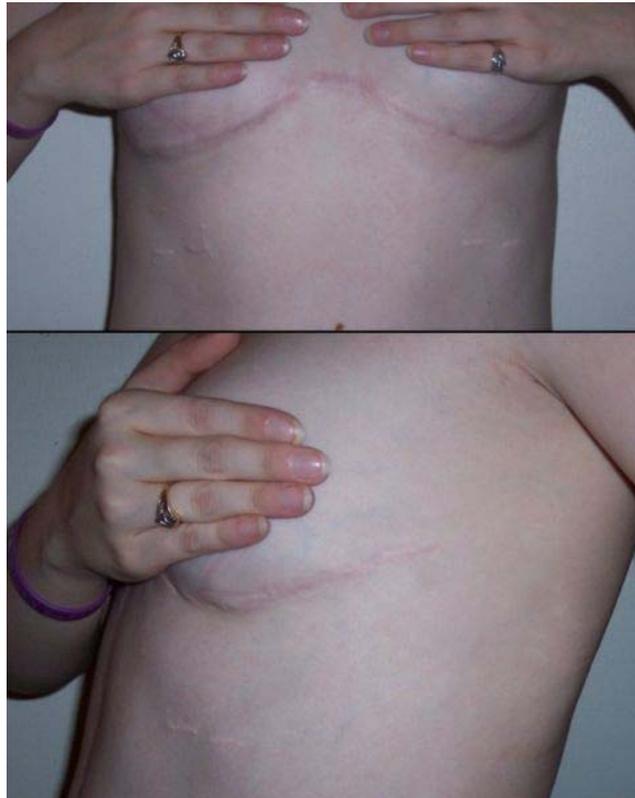
## **Procedure**

While the precise details of surgery will depend on the exact type of transplant, there are many steps which are common to all of these procedures. Prior to operating on the recipient, the transplant surgeon inspects the donor lung(s) for signs of damage or disease. If the lung or lungs are approved, then the recipient is connected to an IV line and various monitoring equipment, including pulse oximetry. The patient will be given general anesthesia, and a machine will breathe for him or her.

It takes about one hour for the pre-operative preparation of the patient. A single lung transplant takes about four to eight hours, while a double lung transplant takes about six to twelve hours to complete. A history of prior chest surgery may complicate the procedure and require additional time.

## **Lobe**

### **Single-lung**



Incision scarring from a double lung transplant

In single-lung transplants, the lung with the worse pulmonary function is chosen for replacement. If both lungs function equally, then the right lung is usually favored for removal because it avoids having to maneuver around the heart, as would be required for excision of the left lung.

In a single-lung transplant the process starts out after the donor lung has been inspected and the decision to accept the donor lung for the patient has been made. An incision is generally made from under the shoulder blade around the chest, ending near the sternum. An alternate method involves an incision under the breastbone. In the case of a singular lung transplant the lung is collapsed, the blood vessels in the lung tied off, and the lung removed at the bronchial tube. The donor lung is placed, the blood vessels reattached, and the lung reinflated. To make sure the lung is satisfactory and to clear any remaining blood and mucus in the new lung a bronchoscopy will be performed. When the surgeons are satisfied with the performance of the lung the chest incision will be closed.

## **Double-lung**

A double-lung transplant, also known as a bilateral transplant, can be executed either sequentially, en bloc, or simultaneously. Sequential is more common than en bloc. This is effectively like having two separate single-lung transplants done.

The transplantation process starts after the donor lungs are inspected and the decision to transplant has been made. An incision is then made from under the patient's armpit, around to the sternum, and then back towards the other armpit; this is known as a clamshell incision. In the case of a sequential transplant the recipient's lung with the poorest lung functions is collapsed, the blood vessels tied off, and cut at the corresponding bronchi. The new lung is then placed and the blood vessels reattached. To make sure the lung is satisfactory before transplanting the other a bronchoscopy is performed. When the surgeons are satisfied with the performance of the new lung, surgery on the second lung will proceed. In 10% to 20% of double-lung transplants the patient is hooked up to a heart-lung machine which pumps blood for the body and supplies fresh oxygen.

## ***Post-operative care***

Immediately following the surgery, the patient is placed in an intensive care unit for monitoring, normally for a period of a few days. The patient is put on a ventilator to assist breathing. Nutritional needs are generally met via total parenteral nutrition, although in some cases a nasogastric tube is sufficient for feeding. Chest tubes are put in so that excess fluids may be removed. Because the patient is confined to bed, a urinary catheter is used. IV lines are used in the neck and arm for monitoring and giving medications. After a few days, barring any complications, the patient may be transferred to a general inpatient ward for further recovery. The average hospital stay following a lung transplant is generally one to three weeks, though complications may require a longer period of time. After this stage, patients are typically required to attend rehabilitation gym for approximately 3 months to regain fitness. Light weights, exercise bike, treadmill, stretches and more are all a part of the rehabilitation programme.

There may be a number of side effects following the surgery. Because certain nerve connections to the lungs are cut during the procedure, transplant recipients cannot feel the urge to cough or feel when their new lungs are becoming congested. They must therefore

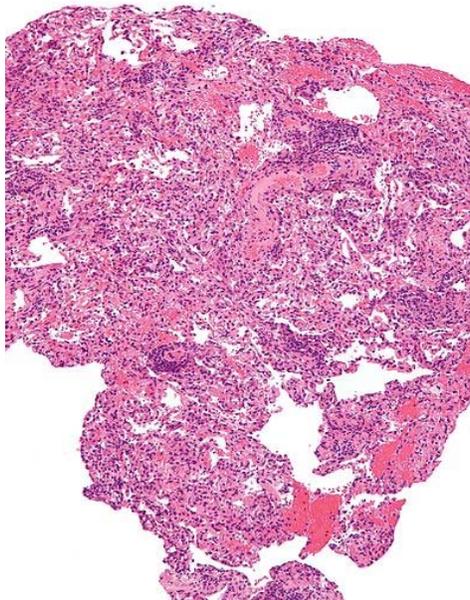
make conscious efforts to take deep breaths and cough in order to clear secretions from the lungs. Their heart rate responds less quickly to exertion due to the cutting of the vagus nerve that would normally help regulate it. They may also notice a change in their voice due to potential damage to the nerves that coordinate the vocal cords.

### ***Miscellaneous***

Post-transplant patients are held from driving for the first 3 months pending an assessment of the patient's capacity to drive; this assessment is usually performed by an occupational therapist. Eyesight, physical ability to do simple actions such as check blind spots, wear a seat belt safely without the wound site being affected and hand eye coordination are all assessed.

Hygiene becomes more important in every day living due to the Immunosuppressant drugs which are required every day to prevent transplant rejection. Lack of a strong immune system leaves transplant recipients vulnerable to infections. Care must be taken into food preparation and hygiene as gastroenteritis becomes more of a risk.

### ***Risks***



Micrograph showing lung transplant rejection. Lung biopsy. H&E stain.

As with any surgical procedure, there are risks of bleeding and infection. The newly transplanted lung itself may fail to properly heal and function. Because a large portion of the patient's body has been exposed to the outside air, sepsis is a possibility, so antibiotics will be given to try to prevent that. Other complications include Post-transplant lymphoproliferative disorder, a form of lymphoma due to the immune suppressants, and gastrointestinal inflammation and ulceration of the stomach and esophagus.

Transplant rejection is a primary concern, both immediately after the surgery and continuing throughout the patient's life. Because the transplanted lung or lungs come from another person, the recipient's immune system will "see" it as an invader and attempt to neutralize it. Transplant rejection is a serious condition and must be treated as soon as possible.

Signs of rejection:

- fever;
- flu-like symptoms, including chills, dizziness, nausea, general feeling of illness, night sweats;
- increased difficulty in breathing;
- worsening pulmonary test results;
- increased chest pain or tenderness;
- increase or decrease in body weight of more than 2 kilograms in a 24-hour period.

In order to prevent transplant rejection and subsequent damage to the new lung or lungs, patients must take a regimen of immunosuppressive drugs. Patients will normally have to take a combination of these medicines in order to combat the risk of rejection. This is a lifelong commitment, and must be strictly adhered to. The immunosuppressive regimen is begun just before or after surgery. Usually the regimen includes cyclosporine, azathioprine and corticosteroids, but as episodes of rejection may reoccur throughout a patient's life, the exact choices and dosages of immunosuppressants may have to be modified over time. Sometimes tacrolimus is given instead of cyclosporine and mycophenolate mofetil instead of azathioprine.

The immunosuppressants that are needed to prevent organ rejection also introduce some risks. By lowering the body's ability to mount an immune reaction, these medicines also increase the chances of infection. Antibiotics may be prescribed in order to treat or prevent such infections. In turn, infection may increase the risk of rejection, and generally an interaction may prevail between both risks. Certain medications may also have nephrotoxic or other potentially harmful side-effects. Other medications may also be prescribed in order to help alleviate these side effects. There is also the risk that a patient may have an allergic reaction to the medications. Close follow-up care is required in order to balance the benefits of these drugs versus their potential risks.

Chronic rejection, meaning repeated bouts of rejection symptoms beyond the first year after the transplant surgery, occurs in approximately 50% of patients. Such chronic rejection presents itself as bronchiolitis obliterans, or less frequently, atherosclerosis.

## ***Prognosis***

These statistics are based on data from 2008. The source data made no distinction between living and deceased donor organs, nor was any distinction made between lobar, single, and double lung transplants.

	<b>1 year survival</b>	<b>5 years survival</b>	<b>10 years survival</b>
Lung transplant	83.6%	53.4%	28.4%
Heart-lung transplant	73.8%	46.5%	28.3%

Transplanted lungs typically last three to five years before showing signs of failure.

## Chapter 11

# Positive Airway Pressure

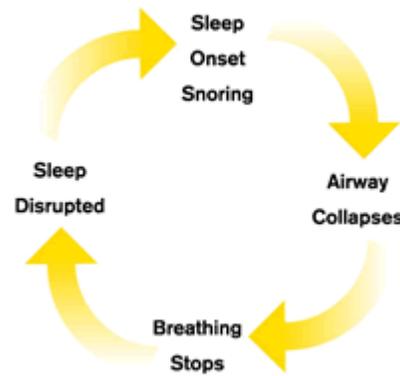


A typical CPAP machine houses the air pump in a case lined with sound-absorbing material for quieter operation. A hose carries the pressurized air to a face mask or nasal pillow.



The Sullivan V Plus, a typical mid-1990s CPAP (the mask is more modern)

### Cycle of Obstructive Sleep Apnea



CPAP therapy breaks the cycle of OSA



A typical full face CPAP mask

**Positive airway pressure (PAP)** is a method of respiratory ventilation used primarily in the treatment of sleep apnea, for which it was first developed. PAP ventilation is also commonly used for those who are critically ill in hospital with respiratory failure, and in newborn infants (neonates). In these patients, PAP ventilation can prevent the need for tracheal intubation, or allow earlier extubation. Sometimes patients with neuromuscular diseases use this variety of ventilation as well. CPAP is an acronym for "continuous positive airway pressure", a variation of the PAP system which was first developed by Professor Colin Sullivan at Royal Prince Alfred Hospital in Sydney, Australia, in 1981.

## ***Indications***

The main indications for positive airway pressure are congestive heart failure and chronic obstructive pulmonary disease. There is some evidence of benefit for those with hypoxia and community acquired pneumonia.

PAP ventilation is often used for patients who have acute type 1 or 2 respiratory failure. Usually PAP ventilation will be reserved for the subset of patients for whom oxygen delivered via a face mask is deemed insufficient or deleterious to health. Usually, patients on PAP ventilation will be closely monitored in an intensive care unit, high dependency unit, coronary care unit or specialist respiratory unit.

The most common conditions for which PAP ventilation is used in hospital are congestive cardiac failure and acute exacerbation of obstructive airway disease, most notably exacerbations of COPD and asthma. It is not used in cases where the airway may be compromised, or consciousness is impaired. CPAP is also used to assist premature babies with breathing in the NICU setting.

The mask required to deliver CPAP must have an effective seal, and be held on very securely. The "nasal pillow" mask maintains its seal by being inserted slightly into the nostrils and being held in place by various straps around the head. Some full-face masks "float" on the face like a hover-craft, with thin, soft, flexible "curtains" ensuring less skin abrasion, and the possibility of coughing and yawning. Some people may find wearing a CPAP mask uncomfortable or constricting. Breathing out against the positive pressure resistance (the expiratory positive airway pressure component, or EPAP) may also be unpleasant to some patients. These factors lead to inability to continue treatment due to patient intolerance in about 20% of cases where it is initiated. Some machines have C-Flex pressure relief technology that makes sleep therapy more comfortable by reducing pressure at the beginning of exhalation and returning to therapeutic pressure just before inhalation. The level of pressure relief varies based on the patient's expiratory flow and which of the three C-Flex settings has been selected, making breathing out against the pressure less difficult. Those who suffer an anxiety disorder or claustrophobia are more likely to be unable to tolerate PAP treatment. Sometimes medication will be given to assist with the anxiety caused by PAP ventilation.

Unlike PAP used at home to splint the tongue and pharynx, PAP is used in hospital to improve the ability of the lungs to exchange oxygen and carbon dioxide, and to decrease the work of breathing (the energy expended moving air into and out of the alveoli). This is because:

- During inspiration, the inspiratory positive airway pressure, or IPAP, forces air into the lungs—thus less work is required from the respiratory muscles.
- The bronchioles and alveoli are prevented from collapsing at the end of expiration. If these small airways and alveoli are allowed to collapse, significant pressures are required to re-expand them. This is because of the Young–Laplace

- equation (which explains why the hardest part of blowing up a balloon is the first breath).
- Entire regions of the lung that would otherwise be collapsed are forced and held open. This process is called recruitment. Usually these collapsed regions of lung will have some blood flow (although reduced). Because these areas of lung are not being ventilated, the blood passing through these areas is not able to efficiently exchange oxygen and carbon dioxide. This is called ventilation–perfusion (or V/Q) mismatch. The recruitment reduces ventilation–perfusion mismatch.
  - The amount of air remaining in the lungs at the end of a breath is greater (this is called the functional residual capacity). The chest and lungs are therefore more expanded. From this more expanded resting position, less work is required to inspire. This is due to the non-linear compliance–volume curve of the lung.

## ***Disadvantages***

A major issue with CPAP is non-compliance. Studies showed that some users either abandon the use of CPAP, and/or use CPAP for only a fraction of the nights.

Prospective PAP candidates are often reluctant to use this therapy, since the nose mask and hose to the machine look uncomfortable and clumsy, and the airflow required for some patients can be vigorous. Some patients will develop nasal congestion while others may experience rhinitis or a runny nose. Some patients adjust to the treatment within a few weeks, others struggle for longer periods, and some discontinue treatment entirely. However, studies show that cognitive behavioral therapy at the beginning of therapy dramatically increases compliance—up to 148%. While PAP side effects are a nuisance, serious side effects are very uncommon. Furthermore, research has shown that PAP side effects are rarely the reason patients stop using PAP. There are reports of dizziness, sinus infections, bronchitis, dry eyes, dry mucosal tissue irritation, ear pain, and nasal congestion secondary to CPAP use.

PAP manufacturers frequently offer different models at different price ranges, and PAP masks have many different sizes and shapes, so that some users need to try several masks before finding a good fit. These different machines may not be comfortable for all users, so proper selection of PAP models may be very important in furthering adherence to therapy.

Beards, mustaches, or facial irregularities may prevent an air-tight seal. Where the mask contacts the skin must be free from dirt and excess chemicals such as skin oils. Shaving before mask-fitting may be necessary.

The CPAP mask can act as an orthodontic headgear and move the teeth and the upper and/or lower jaw backward. This effect can increase over time and may or may not cause TMD disorders in some patients. These facial changes have been dubbed "Smashed Face Syndrome".

## ***Mechanism of action***

### **Continuous pressure devices**

#### **Fixed-pressure CPAP**

A continuous positive airway pressure (CPAP) machine was initially used mainly by patients for the treatment of sleep apnea at home, but now is in widespread use across intensive care units as a form of ventilation. Obstructive sleep apnea occurs when the upper airway becomes narrow as the muscles relax naturally during sleep. This reduces oxygen in the blood and causes arousal from sleep. The CPAP machine stops this phenomenon by delivering a stream of compressed air via a hose to a nasal pillow, nose mask, full-face mask, or hybrid, splinting the airway (keeping it open under air pressure) so that unobstructed breathing becomes possible, therefore reducing and/or preventing apneas and hypopneas. It is important to understand, however, that it is the air pressure, and not the movement of the air, that prevents the apneas. When the machine is turned on, but prior to the mask being placed on the head, a flow of air comes through the mask. After the mask is placed on the head, it is sealed to the face and the air stops flowing. At this point, it is only the air pressure that accomplishes the desired result. This has the additional benefit of reducing or eliminating the extremely loud snoring that sometimes accompanies sleep apnea.

The CPAP machine blows air at a prescribed pressure (also called the titrated pressure). The necessary pressure is usually determined by a sleep physician after review of a study supervised by a sleep technician during an overnight study (polysomnography) in a sleep laboratory. The titrated pressure is the pressure of air at which most (if not all) apneas and hypopneas have been prevented, and it is usually measured in centimetres of water (cm/H<sub>2</sub>O). The pressure required by most patients with sleep apnea ranges between 6 and 14 cm/H<sub>2</sub>O. A typical CPAP machine can deliver pressures between 4 and 20 cm/H<sub>2</sub>O. More specialised units can deliver pressures up to 25 or 30 cm/H<sub>2</sub>O.

CPAP treatment can be highly effective in treatment of obstructive sleep apnea. For some patients, the improvement in the quality of sleep and quality of life due to CPAP treatment will be noticed after a single night's use. Often, the patient's sleep partner also benefits from markedly improved sleep quality, due to the amelioration of the patient's loud snoring.

Given that sleep apnea is a chronic health issue which commonly doesn't go away, ongoing care is usually needed to maintain CPAP therapy. Based on the study of cognitive behavioral therapy (referenced above), ongoing chronic care management is the best way to help patients continue therapy by educating them on the health risks of sleep apnea and providing motivation and support.

## Automatic positive airway pressure

"Automatic positive airway pressure" (APAP, AutoPAP, AutoCPAP) automatically *titrates*, or tunes, the amount of pressure delivered to the patient to the minimum required to maintain an unobstructed airway on a breath-by-breath basis by measuring the resistance in the patient's breathing, thereby giving the patient the precise pressure required at a given moment and avoiding the compromise of fixed pressure.

## Bi-level pressure devices

- "VPAP" or "BiPAP" (variable/bilevel positive airway pressure) provides two levels of pressure: inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP) for easier exhalation. (Some people use the term BPAP to parallel the terms APAP and CPAP.)
  - Modes
    - **S** (Spontaneous) – In spontaneous mode the device triggers IPAP when flow sensors detect spontaneous inspiratory effort and then cycles back to EPAP.
    - **T** (Timed) – In timed mode the IPAP/EPAP cycling is purely machine-triggered, at a set rate, typically expressed in breaths per minute (BPM).
    - **S/T** (Spontaneous/Timed) – Like spontaneous mode, the device triggers to IPAP on patient inspiratory effort. But in spontaneous/timed mode a "backup" rate is also set to ensure that patients still receive a minimum number of breaths per minute if they fail to breathe spontaneously.

## Components

- Flow generator (PAP machine) provides the airflow
- Hose connects the flow generator (sometimes via an in-line humidifier) to the interface
- Interface (nasal or full face mask, nasal pillows, or less commonly a lip-seal mouthpiece) provides the connection to the user's airway

## Optional features

- Humidifier adds moisture to low humidity air
  - Heated: Heated water chamber that can increase patient comfort by eliminating the dryness of the compressed air. The temperature can usually be adjusted or turned off to act as a passive humidifier if desired. In general, a heated humidifier is either integrated into the unit or has a separate power source (i.e. plug).
  - Passive: Air is blown through an unheated water chamber and is dependent on ambient air temperature. It is not as effective as the heated humidifier described above, but still can increase patient comfort by

eliminating the dryness of the compressed air. In general, a passive humidifier is a separate unit and does not have a power source.

- Mask liners: Cloth-based mask liners may be used to prevent excess air leakage and to reduce skin irritation and dermatitis.
- Ramp may be used to temporarily lower the pressure if the user does not immediately sleep. The pressure gradually rises to the prescribed level over a period of time that can be adjusted by the patient and/or the DME provider.
- Exhalation pressure relief: Gives a short drop in pressure during exhalation to reduce the effort required. This feature is known by the trade name C-Flex or A-Flex in some CPAPs made by Respironics and EPR in ResMed machines.
- Flexible chin straps may be used to help the patient not breathe through the mouth (full-face masks avoid this problem), thereby keeping a closed pressure system. The straps are elastic enough that the patient can easily open his mouth if he feels that he needs to. Modern straps use a quick-clip instant fit. Velcro-type adjustments allow quick sizing, before or after the machine is turned on.
- Data logging records basic compliance info or detailed event logging, allowing the sleep physician (or patient) to download and analyse data recorded by the machine to verify treatment effectiveness.
- Automatic altitude adjustment versus manual altitude adjustment.
- DC power source versus AC power source.

Such features generally increase the likelihood of PAP tolerance and compliance.

### ***Care and maintenance***

As with all durable medical equipment, proper maintenance is essential for proper functioning, long unit life and patient comfort. The care and maintenance required for PAP machines varies with the type and conditions of use, and are typically spelled out in a detailed instruction manual specific to the make and model.

Most manufacturers recommend that the end user perform daily and weekly maintenance. Units must be checked regularly for wear and tear and kept clean. Poorly connected, worn or frayed electrical connections may present a shock or fire hazard; worn hoses and masks may reduce the effectiveness of the unit. Most units employ some type of filtration, and the filters must be cleaned or replaced on a regular schedule. Sometimes HEPA filters may be purchased or modified for asthma or other allergy clients. Hoses and masks accumulate exfoliated skin, particulate matter, and can even develop mold. Humidification units must be kept free of mold and algae. Because units use substantial electrical power, housings must be cleaned without immersion.

In cold climates, humidified air may require insulated and/or heated air hoses. These may be bought ready-made, or modified from commonly available materials (aluminium foil and bubble-wrap insulation. Noisy machines may be distanced from the sleeper by extension hoses between the machine and the sleeping person).

Modifications are usually needed by the end-user. Straps are easily twisted wrongly (add hot-melt glue or silicone rubber on the "wrong" side). Fittings and buttons are invisible or without adequate sensation in the darkness of the night, so use bright tape or other fittings (self-adhesive children's earrings, masking tape, etc.) to help prevent mistakes.

### ***Portability***

Since continuous compliance is an important factor in the success of treatment, it is of importance that patients who travel have access to portable equipment. Progressively, PAP units are becoming lighter and more compact, and often come with carrying cases. Dual-voltage power supplies permit many units to be used internationally.

Long-distance travel or camping presents special considerations. Most airport security inspectors have seen the portable machines, so screening rarely presents a special problem. Increasingly, machines are capable of being powered by the 400-Hz power supply used on most commercial aircraft and include manual or automatic altitude adjustment. Some machines allow power-inverter and/or car-battery powering, but polarity of the connecting cables needs consideration.

Some patients on PAP therapy also use supplementary oxygen. When provided in the form of bottled gas, this can present an increased risk of fire and is subject to restrictions. (Commercial airlines generally forbid passengers to bring their own oxygen.) As of November 2006, most airlines permit the use of oxygen concentrators.

## ***Availability***



CPAP flow generator in the back to the left, connected to a 1500 gram preterm newborn by a hose and kept in place on the patient with an improvised interface: a diaper.

In many countries, PAP machines are only available by prescription. A sleep study at an accredited sleep lab is usually necessary before treatment can start. This is because the pressure settings on the PAP machine must be tailored to a patient's treatment needs. A sleep medicine doctor, who may also be trained in respiratory medicine, psychiatry, neurology, paediatrics, family practice or otolaryngology (ear, nose and throat), will interpret the results from the initial sleep study and recommend a pressure test. This may be done in one night (a split study with the diagnostic testing done in the first part of the night, and CPAP testing done in the later part of the night) or with a follow up second

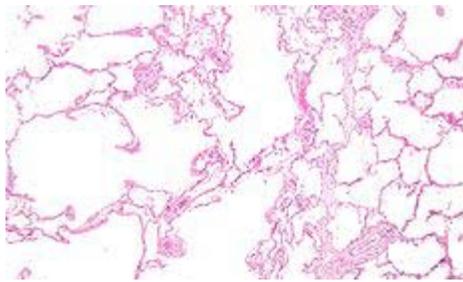
sleep study during which the CPAP titration may be done over the entire night. With CPAP titration (split night or entire night), the patient wears the CPAP mask and pressure is adjusted up and down from the prescribed setting to find the optimal setting.

- In the United States, PAP machines are often available at large discounts online, but a patient purchasing a PAP personally must handle the responsibility of securing reimbursement from his or her insurance or Medicare. Many of the internet providers that deal with insurance such as Medicare will provide upgraded equipment to a patient even if he or she only qualifies for a basic PAP. In some locations a government programme, separate from Medicare, can be used to claim a reimbursement for all or part of the cost of the PAP device.
- In the United Kingdom, PAP machines are available on National Health Service prescription after a diagnosis of sleep apnea or privately from the internet provided a prescription is supplied.
- In Australia, PAP machines can be bought from the Internet or physical stores. There is no requirement for a doctor's prescription, however many suppliers will require a referral. Low-income earners who hold a Commonwealth Health Care Card should enquire with their state's health department about programmes that provide free or low-cost PAP machines. Those who have private health insurance may be eligible for a partial rebate on the cost of a CPAP machine and the mask. Superannuation may be released for the purchase of essential medical equipment such as PAP machines, on the provision of letters from two doctors, one of whom must be a specialist, and an application to the Australian Prudential Regulation Authority (APRA).
- In Canada, CPAP units are widely available in all provinces. Funding for the therapy varies from province to province. In the province of Ontario, the Ministry of Health's Assistive Devices Program will fund a portion of the cost of a CPAP unit based on a sleep study in an approved sleep lab showing Obstructive Sleep Apnea Syndrome and the signature of an approved physician on the application form. This funding is available to all residents of Ontario with a valid health card once every 5 years.

## Chapter 12

# Respiratory Disease

### Respiratory Disease



Micrograph of an emphysematous lung; emphysema is a common respiratory disease, strongly associated with smoking. H&E stain.

**ICD-10** J00.-J99.

**ICD-9** 460-519

**MeSH** D012140

**Respiratory disease** is the term for diseases of the respiratory system. These include diseases of the lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract and of the nerves and muscles of breathing. Respiratory diseases range from mild and self-limiting such as the common cold to life-threatening such as bacterial pneumonia or pulmonary embolism. They are a common and important cause of illness and death. In the US, people suffer 1 billion colds per year. One in seven people in the UK are affected by some form of chronic lung disease, most commonly chronic obstructive pulmonary disease and asthma. Respiratory disease is responsible for over 10% of hospitalizations and over 16% of deaths in Canada (including lung cancer). The study of respiratory disease is known as pulmonology. A doctor who specializes in respiratory disease is known as a pulmonologist, a chest medicine specialist, a respiratory medicine specialist, a respirologist or a thoracic medicine specialist.

## ***Diagnostic tests***

Respiratory diseases may be investigated by performing one or more of the following tests

- Chest x-ray
- Pulmonary function test
- Computed tomography scan
- Culture of microorganisms from secretions such as sputum
- Bronchoscopy
- Biopsy of the lung or pleura
- Ventilation - perfusion scan
- Ultrasound scanning can be useful to detect fluid such as pleural effusion

## ***Treatment for respiratory diseases***

Treatment of respiratory disease depends on the particular disease being treated, the severity of disease and the patient, such as regular exercise and healthy nutrition are important in preventing and treating respiratory disease. Vaccination can prevent some respiratory diseases. In addition, the following treatments are often used for respiratory diseases:

- Medication, often given in an inhaled form
  - Corticosteroids
  - Bronchodilators
  - Antibiotics
  - Anticoagulants
  - Cancer chemotherapy
  - Immune suppressants
- Physiotherapy
- Oxygen
- Mechanical ventilation
- Liquid ventilation (or Liquid breathing)
- Surfactant Replacement Therapy
- Radiotherapy
- Surgery
  - Removal of a cancer e.g. lobectomy, pneumonectomy
  - Pleurodesis
  - Lung volume reduction surgery
  - Lung transplantation
  - Artificial lung

## ***Respiratory diseases***

Respiratory diseases can be classified in many different ways: by the organ involved, by the pattern of symptoms or by the cause of the disease. The main thing is to always be

careful around food because some foods can cause allergic reactions and incite breathing difficulties. Some common examples include sea foods prawns, some fatty fish, raddish, arrow root, ladys finger, lemon, moong dhal, peanuts, water content spinach, curd, bananas, grapes, pomegranates, berries, custard apple, ice creams, etc. In summer, bad weather condition mean sandy and dusty weather or some may affect in winter also.

### **Inflammatory lung disease**

Characterised by a high neutrophil count, eg asthma, cystic fibrosis, emphysema, chronic obstructive pulmonary disorder or acute respiratory distress syndrome.

### **Obstructive lung diseases**

Obstructive lung diseases are diseases of the lung where the bronchial tubes become narrowed making it hard to move air in and especially out of the lung.

### **Chronic Obstructive Pulmonary Disease (COPD)**

Chronic Obstructive Pulmonary Disease (COPD), an example of an obstructive lung disease, is where the airways become damaged, causing them to narrow.

### **Asthma**

Asthma is another example of an obstructive lung disease, (and of an inflammatory lung disease).

### **Restrictive lung diseases**

Restrictive lung diseases (also known as interstitial lung diseases) are a category of respiratory disease characterized by a loss of lung compliance, causing incomplete lung expansion and increased lung stiffness. E.g. in infant respiratory distress syndrome (IRDS).

### **Respiratory tract infections**

Infections can affect any part of the respiratory system. They are traditionally divided into upper respiratory tract infections and lower respiratory tract infections.

### **Upper respiratory tract infection**

The most common upper respiratory tract infection is the common cold however, infections of specific organs of the upper respiratory tract such as sinusitis, tonsillitis, otitis media, pharyngitis and laryngitis are also considered upper respiratory tract infections.

## **Lower respiratory tract infection**

The most common lower respiratory tract infection is pneumonia, a lung infection. Pneumonia is usually caused by bacteria, particularly *Streptococcus pneumoniae* in Western countries. Worldwide, tuberculosis is an important cause of pneumonia. Other pathogens such as viruses and fungi can cause pneumonia for example severe acute respiratory syndrome and pneumocystis pneumonia. A pneumonia may develop complications such as a lung abscess, a round cavity in the lung caused by the infection, or may spread to the pleural cavity.

## **Respiratory tumors**

Tumours of the respiratory system are either malignant or benign.

### **Malignant tumors**

Malignant tumors, or cancers of the respiratory system, particularly lung cancers, are a major health problem responsible for 15% of all cancer diagnoses and 29% of all cancer deaths. The majority of respiratory system cancers are attributable to smoking tobacco.

The major types of respiratory system cancer are:

- Small cell lung cancer
- Non-small cell lung cancer
  - Adenocarcinoma
  - Large cell undifferentiated carcinoma
- Other lung cancers (carcinoid, Kaposi's sarcoma, melanoma)
- Lymphoma
- Head and neck cancer
- Mesothelioma, usually caused by exposure to asbestos dust.

In addition, since many cancers spread via the bloodstream and the entire cardiac output passes through the lungs, it is common for cancer metastases to occur within the lung. Breast cancer may invade directly through local spread, and through lymph node metastases. After metastasis to the liver, colon cancer frequently metastasizes to the lung. Prostate cancer, germ cell cancer and renal cell carcinoma may also metastasize to the lung.

Treatment of respiratory system cancer depends on the type of cancer. Surgery (usually removal of part of the lung, a lobectomy or an entire lung, a pneumonectomy), chemotherapy and radiotherapy are all used. The chance of surviving lung cancer depends on the cancer stage at the time the cancer is diagnosed and is only about 14-17% overall. In the case of metastases to the lung, treatment can occasionally be curative but only in certain, rare circumstances.

## **Benign tumors**

Benign tumors are relatively rare causes of respiratory disease. Examples of benign tumors are:

- Pulmonary hamartoma
- Congenital malformations such as pulmonary sequestration and congenital cystic adenomatoid malformation (CCAM).

## **Pleural cavity diseases**

Pleural cavity diseases include emphysema and mesothelioma which are mentioned above.

A collection of fluid in the pleural cavity is known as a pleural effusion. This may be due to fluid shifting from the bloodstream into the pleural cavity due to conditions such as congestive heart failure and cirrhosis. It may also be due to inflammation of the pleura itself as can occur with infection, pulmonary embolus, tuberculosis, mesothelioma and other conditions.

A pneumothorax is a hole in the pleura covering the lung allowing air in the lung to escape into the pleural cavity. The affected lung “collapses” like a deflated balloon. A tension pneumothorax is a particularly severe form of this condition where the air in the pleural cavity cannot escape, so the pneumothorax keeps getting bigger until it compresses the heart and blood vessels, leading to a life threatening situation.

## **Pulmonary vascular diseases**

Pulmonary vascular diseases are conditions that affect the pulmonary circulation. Examples of these conditions are

- Pulmonary embolism, a blood clot that forms in a vein, breaks free, travels through the heart and lodges in the lungs (thromboembolism). Large pulmonary emboli are fatal, causing sudden death. A number of other substances can also embolise (travel through the blood stream) to the lungs but they are much more rare: fat embolism (particularly after bony injury), amniotic fluid embolism (with complications of labour and delivery), air embolism (iatrogenic - caused by invasive medical procedures).
- Pulmonary arterial hypertension, elevated pressure in the pulmonary arteries. Most commonly it is idiopathic (i.e. of unknown cause) but it can be due to the effects of another disease, particularly COPD. This can lead to strain on the right side of the heart, a condition known as cor pulmonale.
- Pulmonary hemorrhage, inflammation and damage to capillaries in the lung resulting in blood leaking into the alveoli. This may cause blood to be coughed up. Pulmonary hemorrhage can be due to auto-immune disorders such as Wegener's Granulomatosis and Goodpasture's syndrome.

## Chapter 13

# Asthma

### Asthma



Peak flow meters are used to measure one's peak expiratory flow rate

**ICD-10** J45.

**ICD-9** 493

**OMIM** 600807

**DiseasesDB** 1006

**MedlinePlus** 000141

**MeSH** *allergy&field=entry#TreeC08.127.108*  
*C08.127.108*

**Asthma** (from the Greek *ἀσθμα*, *ásthma*, "panting") is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. Symptoms include wheezing, coughing, chest tightness, and shortness of breath.

Treatment of acute symptoms is usually with an inhaled short-acting beta-2 agonist (such as salbutamol). Symptoms can be prevented by avoiding triggers, such as allergens and irritants, and by inhaling corticosteroids. Leukotriene antagonists are less effective than corticosteroids and thus less preferred.

The prevalence of asthma has increased significantly since the 1970s. As of 2009, 300 million people were affected worldwide. In 2009 asthma caused 250,000 deaths globally. Despite this, with proper control of asthma with step down therapy, prognosis is generally good.

## Classification

Clinical classification of severity

Severity in patients $\geq 12$ years of age	Symptom frequency	Nighttime symptoms	%FEV <sub>1</sub> of predicted	FEV <sub>1</sub> Variability	Use of short-acting beta <sub>2</sub> agonist for symptom control (not for prevention of EIB)
<b>Intermittent</b>	$\leq 2$ per week	$\leq 2$ per month	$\geq 80\%$	$< 20\%$	$\leq 2$ days per week
<b>Mild persistent</b>	$> 2$ per week but not daily	3-4 per month	$\geq 80\%$	20–30%	$> 2$ days/week but not daily
<b>Moderate persistent</b>	Daily	$> 1$ per week but not nightly	60–80%	$> 30\%$	Daily
<b>Severe persistent</b>	Throughout the day	Frequent (often 7x/week)	$< 60\%$	$> 30\%$	Several times per day

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV<sub>1</sub>), and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic), based on whether symptoms are precipitated by allergens (atopic) or not (non-atopic).

While asthma is classified based on severity, at the moment there is no clear method for classifying different subgroups of asthma beyond this system. Within the classifications described above, although the cases of asthma respond to the same treatment differs, thus it is clear that the cases within a classification have significant differences. Finding ways to identify subgroups that respond well to different types of treatments is a current critical goal of asthma research.

Although asthma is a chronic obstructive condition, it is not considered as a part of chronic obstructive pulmonary disease as this term refers specifically to combinations of disease that are irreversible such as bronchiectasis, chronic bronchitis, and emphysema.

Unlike these diseases, the airway obstruction in asthma is usually reversible; however, if left untreated, the chronic inflammation of the lungs during asthma can become irreversible obstruction due to airway remodeling. In contrast to emphysema, asthma affects the bronchi, not the alveoli.

## **Brittle asthma**

Brittle asthma is a term used to describe two types of asthma, distinguishable by recurrent, severe attacks. Type 1 brittle asthma refers to disease with wide peak flow variability, despite intense medication. Type 2 brittle asthma describes background well-controlled asthma, with sudden severe exacerbations.

## **Asthma attack**

An acute asthma exacerbation is commonly referred to as an *asthma attack*. The classic symptoms are shortness of breath, wheezing, and chest tightness. While these are the primary symptoms of asthma, some people present primarily with coughing, and in severe cases, air motion may be significantly impaired such that no wheezing is heard.

Signs which occur during an asthma attack include the use of accessory muscles of respiration (sternocleidomastoid and scalene muscles of the neck), there may be a paradoxical pulse (a pulse that is weaker during inhalation and stronger during exhalation), and over-inflation of the chest., a blue color of the skin and nails may occur from lack of oxygen.

In a mild exacerbation the peak expiratory flow rate (PEFR) is  $\geq 200$  L/min or  $\geq 50\%$  of the predicted best. Moderate is defined as between 80 and 200 L/min or 25% and 50% of the predicted best while severe is defined as  $\leq 80$  L/min or  $\leq 25\%$  of the predicted best.

Insufficient levels of vitamin D are linked with severe asthma attacks.

## **Status asthmaticus**

Status asthmaticus is an acute exacerbation of asthma that does not respond to standard treatments of bronchodilators and steroids. Nonselective beta blockers (such as Timolol) have caused fatal status asthmaticus.

## **Exercise induced**

A diagnosis of asthma is common among top athletes. One survey of participants in the 1996 Summer Olympic Games, in Atlanta, Georgia, U.S., showed that 15% had been diagnosed with asthma, and that 10% were on asthma medication.

There appears to be a relatively high incidence of asthma in sports such as cycling, mountain biking, and long-distance running, and a relatively lower incidence in

weightlifting and diving. It is unclear how much of these disparities are from the effects of training in the sport.

Exercise induced asthma can be treated with the use of a short-acting beta2 agonist.

## **Occupational**

Asthma as a result of (or worsened by) workplace exposures is a commonly reported occupational respiratory disease. Still most cases of occupational asthma are not reported or are not recognized as such. Estimates by the American Thoracic Society (2004) suggest that 15–23% of new-onset asthma cases in adults are work related. In one study monitoring workplace asthma by occupation, the highest percentage of cases occurred among operators, fabricators, and laborers (32.9%), followed by managerial and professional specialists (20.2%), and in technical, sales, and administrative support jobs (19.2%). Most cases were associated with the manufacturing (41.4%) and services (34.2%) industries. Animal proteins, enzymes, flour, natural rubber latex, and certain reactive chemicals are commonly associated with work-related asthma. When recognized, these hazards can be mitigated, dropping the risk of disease.

## ***Signs and symptoms***

Common symptoms of asthma include wheezing, shortness of breath, chest tightness and coughing. Symptoms are often worse at night or in the early morning, or in response to exercise or cold air. Some people with asthma only rarely experience symptoms, usually in response to triggers, whereas other may have marked persistent airflow obstruction.

## **Gastro-esophageal reflux disease**

Gastro-esophageal reflux disease coexists with asthma in 80% of people with asthma, with similar symptoms. This is due to increased lung pressures, promoting bronchoconstriction, and through chronic aspiration.

## **Sleep Disorders**

Due to altered anatomy of the respiratory tract: increased upper airway adipose deposition, altered pharynx skeletal morphology, and extension of the pharyngeal airway; leading to upper airway collapse.

## **Cause**

Asthma is caused by environmental and genetic factors. These factors influence how severe asthma is and how well it responds to medication. The interaction is complex and not fully understood.

Studying the prevalence of asthma and related diseases such as eczema and hay fever have yielded important clues about some key risk factors. The strongest risk factor for

developing asthma is a history of atopic disease; this increases one's risk of hay fever by up to 5x and the risk of asthma by 3-4x. In children between the ages of 3-14, a positive skin test for allergies and an increase in immunoglobulin E increases the chance of having asthma. In adults, the more allergens one reacts positively to in a skin test, the higher the odds of having asthma.

Because much allergic asthma is associated with sensitivity to indoor allergens and because Western styles of housing favor greater exposure to indoor allergens, much attention has focused on increased exposure to these allergens in infancy and early childhood as a primary cause of the rise in asthma. Primary prevention studies aimed at the aggressive reduction of airborne allergens in a home with infants have shown mixed findings. Strict reduction of dust mite allergens, for example, reduces the risk of allergic sensitization to dust mites, and modestly reduces the risk of developing asthma up until the age of 8 years old. However, studies also showed that the effects of exposure to cat and dog allergens worked in the converse fashion; exposure during the first year of life was found to *reduce* the risk of allergic sensitization and of developing asthma later in life.

The inconsistency of this data has inspired research into other facets of Western society and their impact upon the prevalence of asthma. One subject that appears to show a strong correlation is the development of asthma and obesity. In the United Kingdom and United States, the rise in asthma prevalence has echoed an almost epidemic rise in the prevalence of obesity. In Taiwan, symptoms of allergies and airway hyper-reactivity increased in correlation with each 20% increase in body-mass index. Several factors associated with obesity may play a role in the pathogenesis of asthma, including decreased respiratory function due to a buildup of adipose tissue (fat) and the fact that adipose tissue leads to a pro-inflammatory state, which has been associated with non-eosinophilic asthma.

Asthma has been associated with Churg–Strauss syndrome, and individuals with immunologically mediated urticaria may also experience systemic symptoms with generalized urticaria, rhino-conjunctivitis, orolaryngeal and gastrointestinal symptoms, asthma, and, at worst, anaphylaxis. Additionally, adult-onset asthma has been associated with periocular xanthogranulomas.

## **Environmental**

Many environmental risk factors have been associated with asthma development and morbidity in children.

Maternal tobacco smoking during pregnancy and after delivery is associated with a greater risk of asthma-like symptoms, wheezing, and respiratory infections during childhood. Low air quality, from traffic pollution or high ozone levels, has been repeatedly associated with increased asthma morbidity and has a suggested association with asthma development that needs further research.

Recent studies show a relationship between exposure to air pollutants (e.g. from traffic) and childhood asthma. This research finds that both the occurrence of the disease and exacerbation of childhood asthma are affected by outdoor air pollutants. High levels of endotoxin exposure may contribute to asthma risk.

Viral respiratory infections are not only one of the leading triggers of an exacerbation but may increase one's risk of developing asthma especially in young children.

Psychological stress has long been suspected of being an asthma trigger, but only in recent decades has convincing scientific evidence substantiated this hypothesis. Rather than stress directly causing the asthma symptoms, it is thought that stress modulates the immune system to increase the magnitude of the airway inflammatory response to allergens and irritants.

Antibiotic use early in life has been linked to development of asthma in several examples; it is thought that antibiotics make children who are predisposed to atopic immune responses susceptible to development of asthma because they modify gut flora, and thus the immune system (as described by the hygiene hypothesis). The hygiene hypothesis is a hypothesis about the cause of asthma and other allergic disease, and is supported by epidemiologic data for asthma. All of these things may negatively affect exposure to beneficial bacteria and other immune system modulators that are important during development, and thus may cause an increased risk for asthma and allergy.

Caesarean sections have been associated with asthma, possibly because of modifications to the immune system (as described by the hygiene hypothesis).

Respiratory infections such as rhinovirus, *Chlamydia pneumoniae* and *Bordetella pertussis* are correlated with asthma exacerbations.

Beta blocker medications such as metoprolol may trigger asthma in those who are susceptible.

Observational studies have found that indoor exposure to volatile organic compounds (VOCs) may be one of the triggers of asthma, however experimental studies have not confirmed these observations. Even VOC exposure at low levels has been associated with an increase in the risk of pediatric asthma. Because there are so many VOCs in the air, measuring total VOC concentrations in the indoor environment may not represent the exposure of individual compounds. Exposure to VOCs is associated with an increase in the IL-4 producing Th2 cells and a reduction in IFN- $\gamma$  producing Th1 cells. Thus the mechanism of action of VOC exposure may be allergic sensitization mediated by a Th2 cell phenotype. Different individual variations in discomfort, from no response to excessive response, were seen in one of the studies. These variations may be due to the development of tolerance during exposure. Another study has concluded that formaldehyde may cause asthma-like symptoms. Low VOC emitting materials should be used while doing repairs or renovations which decreases the symptoms related to asthma caused by VOCs and formaldehyde. In another study "the indoor concentration of

aliphatic compounds (C8-C11), butanols, and 2,2,4-trimethyl 1,3-pentanediol diisobutyrate (TXIB) was significantly elevated in newly painted dwellings. The total indoor VOC was about 100 micrograms/m<sup>3</sup> higher in dwellings painted in the last year". The author concluded that some VOCs may cause inflammatory reactions in the airways and may be the reason for asthmatic symptoms.

There is a significant association between asthma-like symptoms (wheezing) among preschool children and the concentration of DEHP (phthalates) in indoor environment. DEHP (di-ethylhexyl phthalate) is a plasticizer that is commonly used in building material. The hydrolysis product of DEHP (di-ethylhexyl phthalate) is MEHP (Mono-ethylhexyl phthalate) which mimics the prostaglandins and thromboxanes in the airway leading to symptoms related to asthma. Another mechanism that has been studied regarding phthalates causation of asthma is that high phthalates level can "modulate the murine immune response to a coallergen". Asthma can develop in the adults who come in contact with heated PVC fumes. Two main type of phthalates, namely n-butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP), have been associated between the concentration of polyvinyl chloride (PVC) used as flooring and the dust concentrations. Water leakage were associated more with BBzP, and buildings construction were associated with high concentrations of DEHP. Asthma has been shown to have a relationship with plaster wall materials and wall-to wall carpeting. The onset of asthma was also related to the floor-leveling plaster at home. Therefore, it is important to understand the health aspect of these materials in the indoor surfaces.

## Genetic

Over 100 genes have been associated with asthma in at least one genetic association study. However, such studies must be repeated to ensure the findings are not due to chance. Through the end of 2005, 25 genes had been associated with asthma in six or more separate populations:

- GSTM1
- IL10
- CTLA-4
- SPINK5
- LTC4S
- LTA
- GRPA
- NOD1
- CC16
- GSTP1
- STAT6
- NOS1
- CCL5
- TBXA2R
- TGFB1
- IL4
- IL13
- CD14
- ADRB2 ( $\beta$ -2 adrenergic receptor)
- HLA-DRB1
- HLA-DQB1
- TNF
- FCER1B
- IL4R
- ADAM33

Many of these genes are related to the immune system or to modulating inflammation. However, even among this list of highly replicated genes associated with asthma, the results have not been consistent among all of the populations that have been tested. This indicates that these genes are not associated with asthma under every condition, and that researchers need to do further investigation to figure out the complex interactions that cause asthma. One theory is that asthma is a collection of several diseases, and that genes might have a role in only subsets of asthma. For example, one group of genetic

differences (single nucleotide polymorphisms in 17q21) was associated with asthma that develops in childhood.

## Gene–environment interactions

CD14-endotoxin interaction based on CD14 SNP C-159T

Endotoxin levels	CC genotype	TT genotype
High exposure	Low risk	High risk
Low exposure	High risk	Low risk

Research suggests that some genetic variants may only cause asthma when they are combined with specific environmental exposures, and otherwise may not be risk factors for asthma.

The genetic trait, CD14 single nucleotide polymorphism (SNP) C-159T and exposure to endotoxin (a bacterial product) are a well-replicated example of a gene-environment interaction that is associated with asthma. Endotoxin exposure varies from person to person and can come from several environmental sources, including environmental tobacco smoke, dogs, and farms. Researchers have found that risk for asthma changes based on a person's genotype at CD14 C-159T and level of endotoxin exposure.

## Exacerbation

Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma. Different asthmatic individuals react differently to various factors. However, most individuals can develop severe exacerbation of asthma from several triggering agents.

Home factors that can lead to exacerbation include dust, house mites, animal dander (especially cat and dog hair), cockroach allergens and molds at any given home. Perfumes are a common cause of acute attacks in females and children. Both virus and bacterial infections of the upper respiratory tract infection can worsen asthma.

## Hygiene hypothesis

One theory for the cause of the increase in asthma prevalence worldwide is the "hygiene hypothesis" —that the rise in the prevalence of allergies and asthma is a direct and unintended result of reduced exposure to a wide variety of different bacteria and virus types in modern societies, or modern hygienic practices preventing childhood infections. Children living in less hygienic environments (East Germany vs. West Germany, families with many children, day care environments) tend to have lower incidences of asthma and allergic diseases. This seems to run counter to the logic that viruses are often causative agents in exacerbation of asthma. Additionally, other studies have shown that viral infections of the lower airway may in some cases *induce* asthma, as a history of bronchiolitis or croup in early childhood is a predictor of asthma risk in later life. Studies which show that upper respiratory tract infections are protective against asthma risk also

tend to show that lower respiratory tract infections conversely tend to increase the risk of asthma.

### Socioeconomic factors

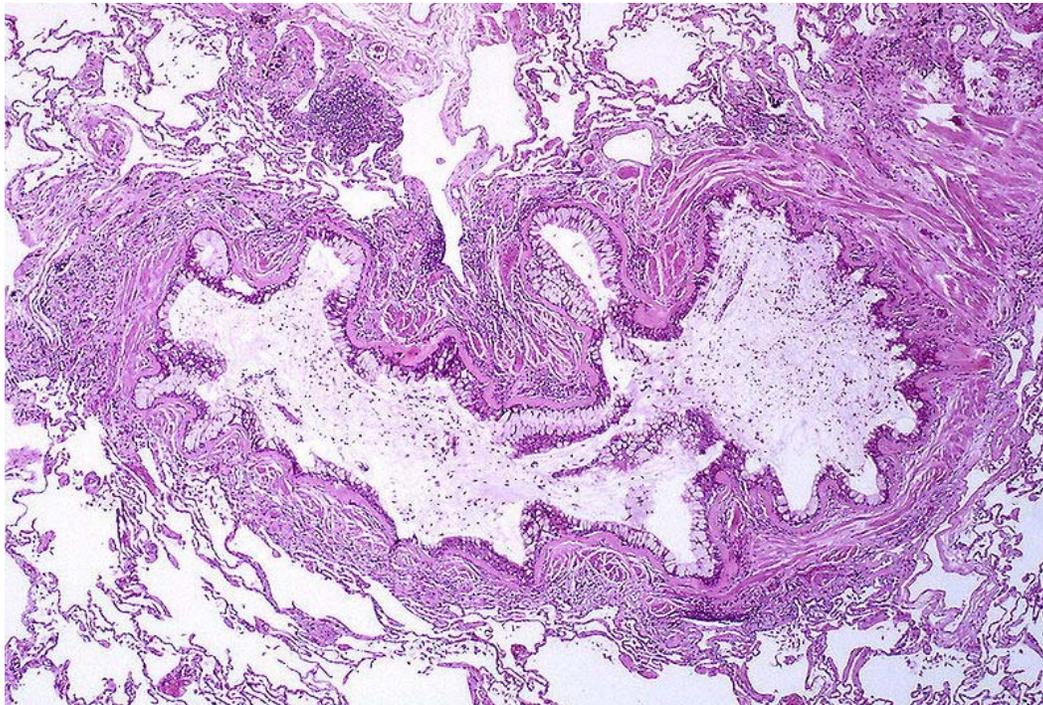
The incidence of asthma is highest among low-income populations worldwide. Asthma deaths are most common in low and middle income countries, and in the Western world, it is found in those low-income neighborhoods whose populations consist of large percentages of ethnic minorities. Additionally, asthma has been strongly associated with the presence of cockroaches in living quarters; these insects are more likely to be found in those same neighborhoods.

Most likely due to income and geography, the incidence of and treatment quality for asthma varies among different racial groups. The prevalence of "severe persistent" asthma is also greater in low-income communities than those with better access to treatment.

### Diagnosis

Severity of acute asthma exacerbations		
<b>Near-fatal asthma</b>	High PaCO <sub>2</sub> and/or requiring mechanical ventilation	
<b>Life threatening asthma</b>	Any one of the following in a person with severe asthma:-	
	<b>Clinical signs</b>	<b>Measurements</b>
	Altered level of consciousness	Peak flow < 33%
	Exhaustion	Oxygen saturation < 92%
	Arrhythmia	PaO <sub>2</sub> < 8 kPa
	Low blood pressure	"Normal" PaCO <sub>2</sub>
	Cyanosis	
	Silent chest	
	Poor respiratory effort	
<b>Acute severe asthma</b>	Any one of:-	
	Peak flow 33-50%	
	Respiratory rate ≥ 25 breaths per minute	

	Heart rate $\geq$ 110 beats per minute
	Unable to complete sentences in one breath
<b>Moderate asthma exacerbation</b>	Worsening symptoms
	Peak flow 80%-50% best or predicted
	No features of acute severe asthma



Obstruction of the lumen of the bronchiole by mucoid exudate, goblet cell metaplasia, epithelial basement membrane thickening and severe inflammation of bronchiole in a patient with asthma.

There is currently not a precise physiologic, immunologic, or histologic test for diagnosing asthma. The diagnosis is usually made based on the pattern of symptoms (airways obstruction and hyperresponsiveness) and/or response to therapy (partial or complete reversibility) over time.

The British Thoracic Society determines a diagnosis of asthma using a ‘response to therapy’ approach. If the patient responds to treatment, then this is considered to be a confirmation of the diagnosis of asthma. The response measured is the reversibility of airway obstruction after treatment. Airflow in the airways is measured with a peak flow meter or spirometer, and the following diagnostic criteria are used by the British Thoracic Society:

- $\geq 20\%$  difference on at least three days in a week for at least two weeks;
- $\geq 20\%$  improvement of peak flow following treatment, for example:
  - 10 minutes of inhaled  $\beta$ -agonist (e.g., salbutamol);
  - six weeks of inhaled corticosteroid (e.g., beclometasone);
  - 14 days of 30 mg prednisolone.
- $\geq 20\%$  decrease in peak flow following exposure to a trigger (e.g., exercise).

In contrast, the US National Asthma Education and Prevention Program (NAEPP) uses a ‘symptom patterns’ approach. Their guidelines for the diagnosis and management of asthma state that a diagnosis of asthma begins by assessing if any of the following list of indicators is present. While the indicators are not sufficient to support a diagnosis of asthma, the presence of multiple key indicators increases the probability of a diagnosis of asthma. Spirometry is needed to establish a diagnosis of asthma.

- Wheezing—high-pitched whistling sounds when breathing out—especially in children. (Lack of wheezing and a normal chest examination do not exclude asthma.)
- history of any of the following:
  - Cough, worse particularly at night
  - Recurrent wheeze
  - Recurrent difficulty in breathing
  - Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection
  - Animals with fur or hair
  - House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - Mold
  - Smoke (tobacco, wood)
  - Pollen
  - Changes in weather
  - Strong emotional expression (laughing or crying hard)
  - Airborne chemicals or dusts
  - Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient

The latest guidelines from the U.S. National Asthma Education and Prevention Program (NAEPP) recommend spirometry at the time of initial diagnosis, after treatment is initiated and symptoms are stabilized, whenever control of symptoms deteriorates, and every 1 or 2 years on a regular basis. The NAEPP guidelines do not recommend testing peak expiratory flow as a regular screening method because it is more variable than spirometry. However, testing peak flow at rest (or baseline) and after exercise can be helpful, especially in young patients who may experience only exercise-induced asthma. It may also be useful for daily self-monitoring and for checking the effects of new medications. Peak flow readings can be charted together with a record of symptoms or

use peak flow charting software. This allows patients to track their peak flow readings and pass information back to their doctor or nurse.

## Differential diagnosis

Differential diagnoses include:

- Infants and Children
  - Upper airway diseases
    - Allergic rhinitis and sinusitis
  - Obstructions involving large airways
    - Foreign body in trachea or bronchus
    - Vocal cord dysfunction
    - Vascular rings or laryngeal webs
    - Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
    - Enlarged lymph nodes or tumor
  - Obstructions involving small airways
    - Viral bronchiolitis or obliterative bronchiolitis
    - Cystic fibrosis
    - Bronchopulmonary dysplasia
    - Heart disease
  - Other causes
    - Recurrent cough not due to asthma
    - Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux
    - Medication induced
- Adults
  - COPD (e.g., chronic bronchitis or emphysema)
  - Congestive heart failure
  - Pulmonary embolism
  - Mechanical obstruction of the airways (benign and malignant tumors)
  - Pulmonary infiltration with eosinophilia
  - Cough secondary to drugs (e.g., angiotensin-converting enzyme (ACE) inhibitors)
  - Vocal cord dysfunction

Before diagnosing asthma, alternative possibilities should be considered such as the use of known bronchoconstrictors (substances that cause narrowing of the airways, e.g. certain anti-inflammatory agents or beta-blockers). Among elderly people, the presenting symptom may be fatigue, cough, or difficulty breathing, all of which may be erroneously attributed to Chronic obstructive pulmonary disease(COPD), congestive heart failure, or simple aging.

## **Chronic Obstructive Pulmonary Disease**

Chronic obstructive pulmonary disease can coexist with asthma and can occur as a complication of chronic asthma. After the age of 65 most people with obstructive airway disease will have asthma and COPD. In this setting, COPD can be differentiated by increased airway neutrophils, abnormally increased wall thickness, and increased smooth muscle in the bronchi. However, this level of investigation is not performed due to COPD and asthma sharing similar principles of management: corticosteroids, long acting beta agonists, and smoking cessation. It closely resembles asthma in symptoms, is correlated with more exposure to cigarette smoke, an older age, less symptom reversibility after bronchodilator administration (as measured by spirometry), and decreased likelihood of family history of atopy.

### **Others**

The term "atopy" was coined to describe this triad of atopic eczema, allergic rhinitis and asthma.

Pulmonary aspiration, whether direct due to dysphagia (swallowing disorder) or indirect (due to acid reflux), can show similar symptoms to asthma. However, with aspiration, fevers might also indicate aspiration pneumonia. Direct aspiration (dysphagia) can be diagnosed by performing a modified barium swallow test. If the aspiration is indirect (from acid reflux), then treatment is directed at this is indicated.

### **Prevention**

The evidence for the effectiveness of measures to prevent the development of asthma is weak. Ones which show some promise include: limiting smoke exposure both in utero and after delivery, breastfeeding, increased exposure to respiratory infection per the hygiene hypothesis (such as in those who attend daycare or are from large families).

### **Management**

A specific, customized plan for proactively monitoring and managing symptoms should be created. Someone who has asthma should understand the importance of reducing exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan should be written down and adjusted according to changes in symptoms.

The most effective treatment for asthma is identifying triggers, such as cigarette smoke, pets, or aspirin, and eliminating exposure to them. If trigger avoidance is insufficient, medical treatment is recommended. Medical treatments used depends on the severity of illness and the frequency of symptoms. Specific medications for asthma are broadly classified in to fast acting and long acting.

Bronchodilators are recommended for short-term relief of symptoms. In those with occasional attacks, no other medication is needed. If mild persistent disease is present (more than two attacks a week), low-dose inhaled glucocorticoids or alternatively, an oral leukotriene antagonist or a mast cell stabilizer is recommended. For those who suffer daily attacks, a higher dose of inhaled glucocorticoid is used. In a severe asthma exacerbation, oral glucocorticoids are added to these treatments.

## Lifestyle modification

Avoidance of triggers is a key component of improving control and preventing attacks. The most common triggers include: allergens, smoke (tobacco and other), air pollution, non selective beta-blockers, and sulfite-containing foods.

## Medications

Medications used to treat asthma are divided into two general classes: quick-relief medications used to treat acute symptoms; and long-term control medications used to prevent further exacerbation.

Fast acting



Salbutamol metered dose inhaler commonly used to treat asthma attacks

- Short acting beta<sub>2</sub>-adrenoceptor agonists (SABA), such as salbutamol (*albuterol* USAN) are the first line treatment for asthma symptoms.
- Anticholinergic medications, such as ipratropium bromide provide addition benefit when used in combination with SABA in those with moderate or severe symptoms. Anticholinergic bronchodilators can also be used if a person cannot tolerate a SABA.
- Older, less selective adrenergic agonists, such as inhaled epinephrine, have similar efficacy to SABAs. They are however not recommended due to concerns regarding excessive cardiac stimulation.

#### Long term control



Fluticasone propionate metered dose inhaler commonly used for long term control

- Glucocorticoids are the most effective treatment available for long term control. Inhaled forms are usually used except in the case of severe persistent disease, in which oral steroids may be needed. Inhaled formulations may be used once or twice daily, depending on the severity of symptoms.

- Long acting beta-adrenoceptor agonists (LABA) have at least a 12-hour effect. They are however not to be used without a steroid due to an increased risk of severe symptoms. In December 2008, members of the FDA's drug-safety office recommended withdrawing approval for these medications in children. Discussion is ongoing about their use in adults.
- Leukotriene antagonists (such as zafirlukast) are an alternative to inhaled glucocorticoids, but are not preferred. They may also be used in addition to inhaled glucocorticoids but in this role are second line to LABA.
- Mast cell stabilizers (such as cromolyn sodium) are another non-preferred alternative to glucocorticoids.

### Delivery methods

Medications are typically provided as metered-dose inhalers (MDIs) in combination with an asthma spacer or as a dry powder inhaler. The spacer is a plastic cylinder that mixes the medication with air, making it easier to receive a full dose of the drug. A nebulizer may also be used. Nebulizers and spacers are equally effective in those with mild to moderate symptoms however insufficient evidence is available to determine whether or not a difference exist in those severe symptomatology.

### Safety and adverse effects

Long-term use of glucocorticoids carries a significant potential for adverse effects. The incidence of cataracts is increased in people undergoing treatment for asthma with corticosteroids, due to altered regulation of lens epithelial cells. The incidence of osteoporosis is also increased, due to changes in bone remodeling.

### Other

When an asthma attack is unresponsive to usual medications, other options are available for emergency management.

- Oxygen is used to alleviate hypoxia if saturations fall below 92%.
- Magnesium sulfate intravenous treatment has been shown to provide a bronchodilating effect when used in addition to other treatment in severe acute asthma attacks.
- Heliox, a mixture of helium and oxygen, may also be considered in severe unresponsive cases.
- Intravenous salbutamol is not supported by available evidence and is thus used only in extreme cases.
- Methylxanthines (such as theophylline) were once widely used, but do not add significantly to the effects of inhaled beta-agonists.
- The dissociative anesthetic ketamine is theoretically useful if intubation and mechanical ventilation is needed in people who are approaching respiratory arrest; however, there is no evidence from clinical trials to support this.

## **Complementary medicine**

Many asthma patients, like those who suffer from other chronic disorders, use alternative treatments; surveys show that roughly 50% of asthma patients use some form of unconventional therapy. There is little data to support the effectiveness of most of these therapies. Evidence is insufficient to support the usage of Vitamin C. Acupuncture is not recommended for the treatment as there is insufficient evidence to support its use. Air ionisers show no evidence that they improve asthma symptoms or benefit lung function; this applied equally to positive and negative ion generators.

Dust mite control measures, including air filtration, chemicals to kill mites, vacuuming, mattress covers and others methods had no effect on asthma symptoms. However, a review of 30 studies found that "bedding encasement might be an effective asthma treatment under some conditions" (when the patient is highly allergic to dust mite and the intervention reduces the dust mite exposure level from high levels to low levels). Washing laundry/rugs in hot water was also found to improve control of allergens.

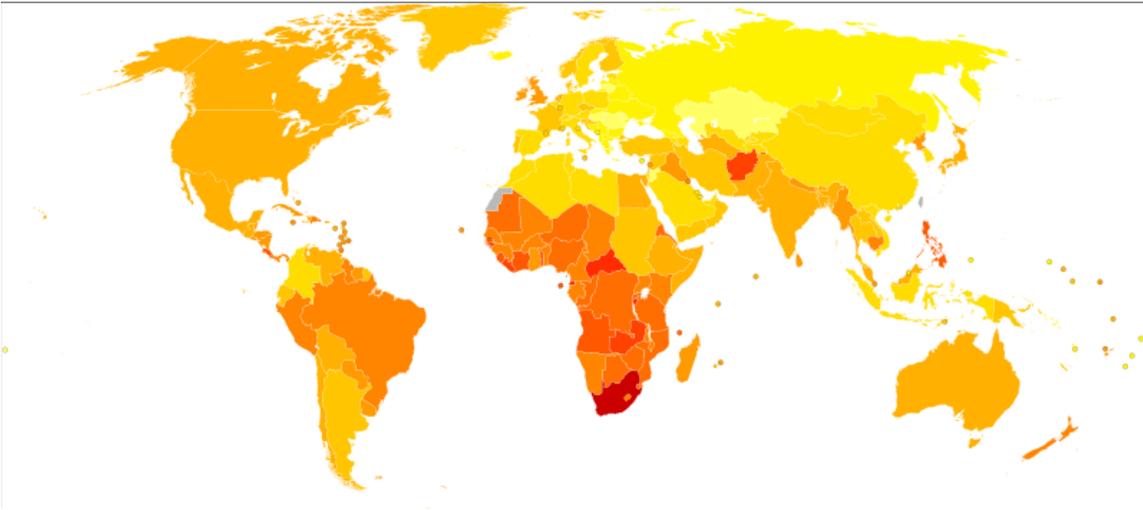
A study of "manual therapies" for asthma, including osteopathic, chiropractic, physiotherapeutic and respiratory therapeutic manoeuvres, found there is insufficient evidence to support or refute their use in treating. The Buteyko breathing technique for controlling hyperventilation may result in a reduction in medications use however does not have any effect on lung function. Thus an expert panel felt that evidence was insufficient to support its use.

## ***Prognosis***

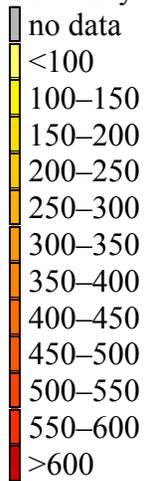
The prognosis for asthma is good, especially for children with mild disease. Of asthma diagnosed during childhood, 54% of cases will no longer carry the diagnosis after a decade. The extent of permanent lung damage in people with asthma is unclear. Airway remodeling is observed, but it is unknown whether these represent harmful or beneficial changes. Although conclusions from studies are mixed, most studies show that early treatment with glucocorticoids prevents or ameliorates decline in lung function as measured by several parameters. For those who continue to suffer from mild symptoms, corticosteroids can help most to live their lives with few disabilities. It is more likely to consider immediate medication of inhaled corticosteroids as soon as asthma attacks occur. According to studies conducted, patients with relatively mild asthma who have received inhaled corticosteroids within 12 months of their first asthma symptoms achieved good functional control of asthma after 10 years of individualized therapy as compared to patients who received this medication after 2 years (or more) from their first attacks. Though they (delayed) also had good functional control of asthma, they were observed to exhibit slightly less optimal disease control and more signs of airway inflammation.

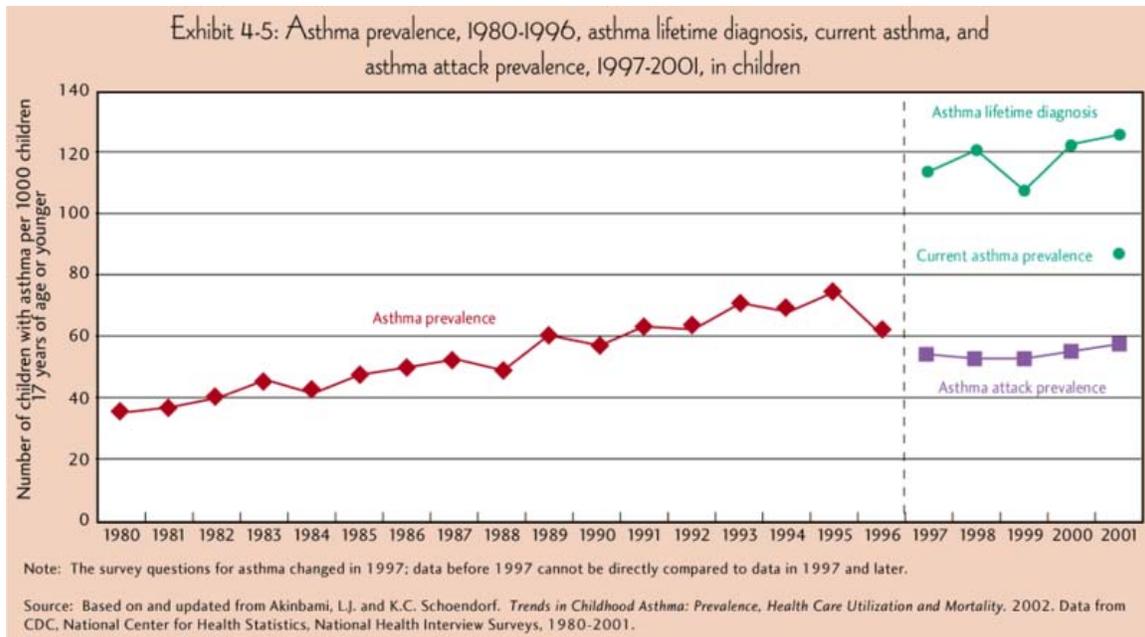
Asthma mortality has decreased over the last few decades due to better recognition and improvement in care.

## Epidemiology



Disability-adjusted life year for asthma per 100,000 inhabitants in 2004.





The prevalence of childhood asthma in the United States has increased since 1980, especially in younger children.

As of 2009, 300 million people worldwide were affected by asthma leading to approximately 250,000 deaths per year.

It is estimated that asthma has a 7-10% prevalence worldwide. As of 1998, there was a great disparity in prevalence worldwide across the world (as high as a 20 to 60-fold difference), with a trend toward more developed and westernized countries having higher rates of asthma. Westernization however does not explain the entire difference in asthma prevalence between countries, and the disparities may also be affected by differences in genetic, social and environmental risk factors. Mortality however is most common in low to middle income countries, while symptoms were most prevalent (as much as 20%) in the United Kingdom, Australia, New Zealand, and Republic of Ireland; they were lowest (as low as 2-3%) in Eastern Europe, Indonesia, Greece, Uzbekistan, India, and Ethiopia.

While asthma is more common in affluent countries, it is by no means a restricted problem; the WHO estimate that there are between 15 and 20 million people with asthma in India. In the U.S., urban residents, Hispanics, and African Americans are affected more than the population as a whole. Striking increases in asthma prevalence have been observed in populations migrating from a rural environment to an urban one, or from a third-world country to Westernized one.

Asthma affects approximately 7% of the population of the United States and 5% of people in the United Kingdom. Asthma causes 4,210 deaths per year in the United States. In 2005 in the United States asthma affected more than 22 million people including 6 million children. It accounted for nearly 1/2 million hospitalizations. More boys have asthma than girls, but more women have it than men. Of all children, African Americans

and Latinos who live in cities are more at risk for developing asthma. African American children in the U.S. are four times more likely to die of asthma and three times more likely to be hospitalized, compared to their white counterparts. In some Latino neighborhoods, as many as one in three children has been found to have asthma.

In England, an estimated 261,400 people were newly diagnosed with asthma in 2005; 5.7 million people had an asthma diagnosis and were prescribed 32.6 million asthma-related prescriptions.

The frequency of atopic dermatitis, asthma, urticaria and allergic contact dermatitis has been found to be lower in psoriatic patients.

### **Increasing frequency**

Rates of asthma have increased significantly between the 1960s and 2008. Some 9% of US children had asthma in 2001, compared with just 3.6% in 1980. The World Health Organization (WHO) reports that some 10% of the Swiss population suffers from asthma today, compared with just 2% some 25–30 years ago.

### **Variability**

Asthma prevalence in the US is higher than in most other countries in the world, but varies drastically between diverse US populations. In the US, asthma prevalence is highest in Puerto Ricans, African Americans, Filipinos, Irish Americans, and Native Hawaiians, and lowest in Mexicans and Koreans. Mortality rates follow similar trends, and response to salbutamol is lower in Puerto Ricans than in African Americans or Mexicans. As with worldwide asthma disparities, differences in asthma prevalence, mortality, and drug response in the US may be explained by differences in genetic, social and environmental risk factors.

Asthma prevalence also differs between populations of the same ethnicity who are born and live in different places. US-born Mexican populations, for example, have higher asthma rates than non-US born Mexican populations that are living in the US.

There is no correlation between asthma and gender in children. More adult women are diagnosed with asthma than adult men, but this does not necessarily mean that more adult women have asthma.

### **History**

Asthma was first recognized and named by Hippocrates circa 450 BC. During the 1930s–50s, asthma was considered as being one of the 'holy seven' psychosomatic illnesses. Its aetiology was considered to be psychological, with treatment often based on psychoanalysis and other 'talking cures'. As these psychoanalysts interpreted the asthmatic wheeze as the suppressed cry of the child for its mother, so they considered that the treatment of depression was especially important for individuals with asthma.

## ***Research***

- The University of Maryland School of Medicine announced in 2010 that bitter taste receptors had been discovered on smooth muscle in human lung bronchi. These smooth muscles control airway contraction and dilation - contrary to expectation, bitter substances such as quinine or chloroquine opened contracted airways, offering new insight into asthma.

## Chapter 14

# Lung Cancer

### Lung Cancer



Cross section of a human lung. The white area in the upper lobe is cancer; the black areas are discoloration due to smoking.

**ICD-10** C33.-C34.

**ICD-9** 162

**DiseasesDB** 7616

**MedlinePlus** 007194

**eMedicine** med/1333 med/1336 emerg/335  
radio/807 radio/405 radio/406

**MeSH** D002283

**Lung cancer** is a disease which consists of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas, derived from epithelial cells. Lung cancer, the most common cause of cancer-related death in men and women, is responsible for 1.3 million deaths worldwide annually, as of 2004. The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss.

The main types of lung cancer are *small-cell lung carcinoma* and *non-small-cell lung carcinoma*. This distinction is important, because the treatment varies; non-small-cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small-cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation. The most common cause of lung cancer is long-term exposure to tobacco smoke. The occurrence of lung cancer in nonsmokers, who account for as many as 15% of cases, is often attributed to a combination of genetic factors, radon gas, asbestos, and air pollution including secondhand smoke.

Lung cancer may be seen on chest radiograph and computed tomography (CT scan). The diagnosis is confirmed with a biopsy. This is usually performed by bronchoscopy or CT-guided biopsy. Treatment and prognosis depend upon the histological type of cancer, the stage (degree of spread), and the patient's performance status. Possible treatments include surgery, chemotherapy, and radiotherapy. Survival varies, depending on stage, overall health, and other factors, but the overall five-year survival rate for all persons diagnosed with lung cancer is 14%.

## ***Signs and symptoms***

Symptoms that suggest lung cancer include:

- dyspnea (shortness of breath)
- hemoptysis (coughing up blood)
- chronic coughing or change in regular coughing pattern
- wheezing
- chest pain or pain in the abdomen
- cachexia (weight loss), fatigue, and loss of appetite
- dysphonia (hoarse voice)
- clubbing of the fingernails (uncommon)
- dysphagia (difficulty swallowing).

If the cancer grows in the airway, it may obstruct airflow, causing breathing difficulties. The obstruction can lead to accumulation of secretions behind the blockage, and predispose to pneumonia. Many lung cancers have a rich blood supply. The surface of the cancer may be fragile, leading to bleeding from the cancer into the airway. This blood may subsequently be coughed up.

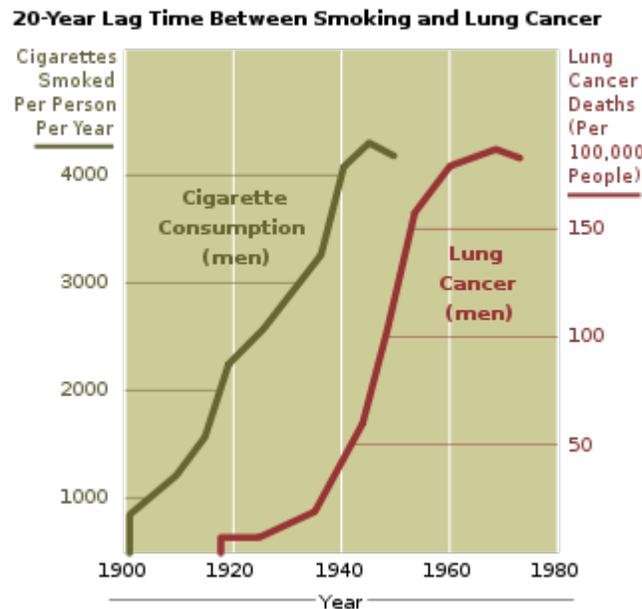
Depending on the type of tumor, so-called paraneoplastic phenomena may initially attract attention to the disease. In lung cancer, these phenomena may include Lambert-Eaton myasthenic syndrome (muscle weakness due to auto-antibodies), hypercalcemia, or syndrome of inappropriate antidiuretic hormone (SIADH). Tumors in the top (apex) of the lung, known as Pancoast tumors, may invade the local part of the sympathetic nervous system, leading to changed sweating patterns and eye muscle problems (a combination known as Horner's syndrome) as well as muscle weakness in the hands due to invasion of the brachial plexus.

Many of the symptoms of lung cancer (bone pain, fever, and weight loss) are nonspecific; in the elderly, these may be attributed to comorbid illness. In many patients, the cancer has already spread beyond the original site by the time they have symptoms and seek medical attention. Common sites of metastasis include the brain, bone, adrenal glands, contralateral (opposite) lung, liver, pericardium, and kidneys. About 10% of people with lung cancer do not have symptoms at diagnosis; these cancers are incidentally found on routine chest radiograph.

## Causes

The main causes of any cancer include carcinogens (such as those in tobacco smoke), ionizing radiation, and viral infection. This exposure causes cumulative changes to the DNA in the tissue lining the bronchi of the lungs (the bronchial epithelium). As more tissue becomes damaged, eventually a cancer develops.

## Smoking



NIH graph showing the correlation and time-lag between tobacco smoking and lung cancer rate in the U.S. male population.

Smoking, particularly of cigarettes, is by far the main contributor to lung cancer. Cigarette smoke contains over 60 known carcinogens, including radioisotopes from the radon decay sequence, nitrosamine, and benzopyrene. Additionally, nicotine appears to depress the immune response to malignant growths in exposed tissue. Across the developed world, almost 90% of lung cancer deaths are caused by smoking. In the United States, smoking is estimated to account for 87% of lung cancer cases (90% in men and 85% in women). Among male smokers, the lifetime risk of developing lung cancer is 17.2%; among female smokers, the risk is 11.6%. This risk is significantly lower in nonsmokers: 1.3% in men and 1.4% in women.

Women who smoke (former smokers and current smokers) and take hormone therapy are at a much higher risk of dying of lung cancer. In a study by Chlebowski *et al.* published in 2009, the women taking hormones were about 60% more likely to die of lung cancer than the women taking a placebo. Not surprisingly, the risk was highest for current smokers, followed by past smokers, and lowest for never smokers. Among the women who smoked (former or current smokers), 3.4% of those taking hormone therapy died of lung cancer compared to 2.3% for women taking the placebo.

The time a person smokes (as well as rate of smoking) increases the person's chance of developing lung cancer. If a person stops smoking, this chance steadily decreases as damage to the lungs is repaired and contaminant particles are gradually removed. In addition, there is evidence that lung cancer in never-smokers has a better prognosis than in smokers, and that patients who smoke at the time of diagnosis have shorter survival times than those who have quit.

Passive smoking—the inhalation of smoke from another's smoking—is a cause of lung cancer in nonsmokers. A passive smoker can be classified as someone living or working with a smoker. Studies from the U.S., Europe, the UK, and Australia have consistently shown a significant increase in relative risk among those exposed to passive smoke. Recent investigation of sidestream smoke suggests that it is more dangerous than direct smoke inhalation.

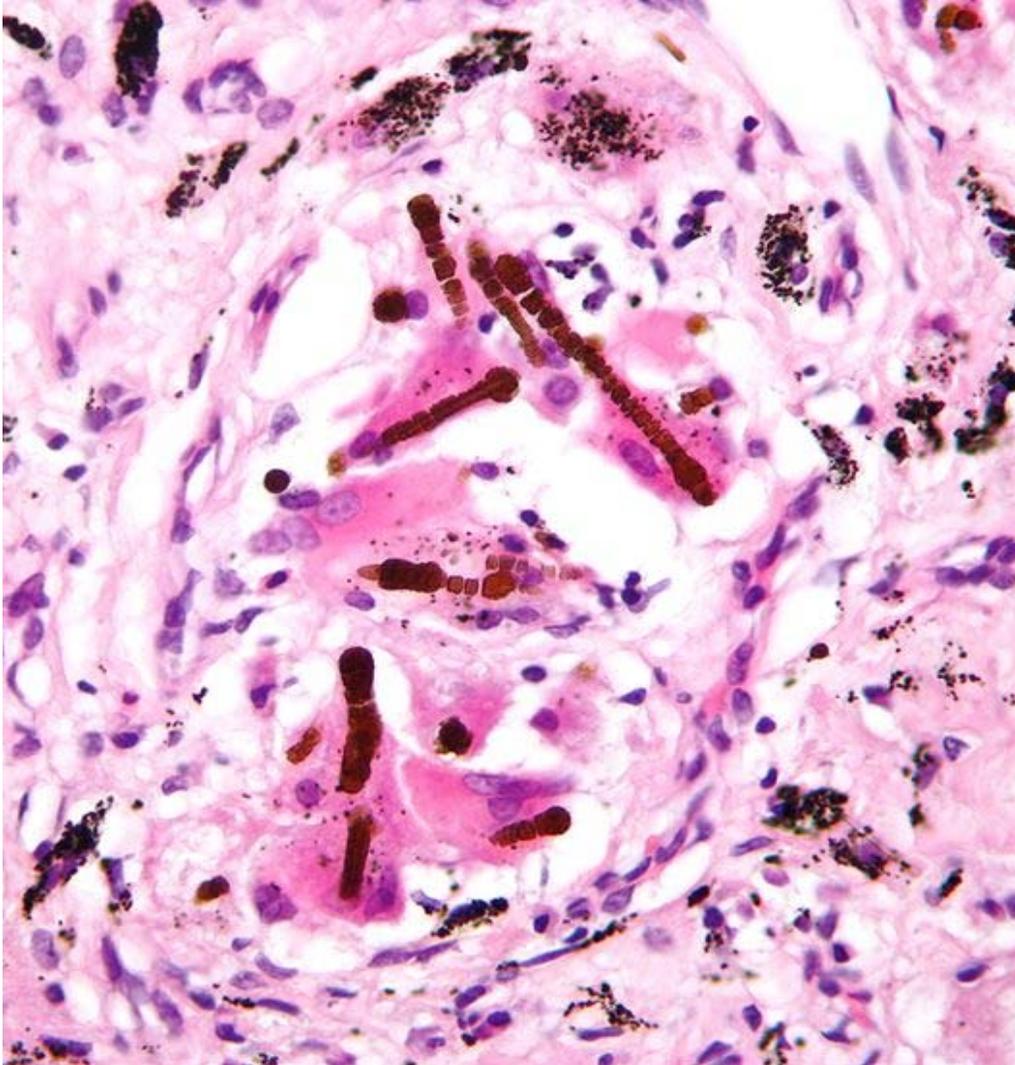
10–15% of lung cancer patients have never smoked. That means between 20,000 to 30,000 never-smokers are diagnosed with lung cancer in the United States each year. Because of the five-year survival rate, each year in the U.S. more never-smokers die of lung cancer than do patients of leukemia, ovarian cancer, or AIDS.

## **Radon gas**

Radon is a colorless and odorless gas generated by the breakdown of radioactive radium, which in turn is the decay product of uranium, found in the Earth's crust. The radiation decay products ionize genetic material, causing mutations that sometimes turn cancerous. Radon exposure is the second major cause of lung cancer in the general population, after smoking with the risk increasing by 8% to 16% for every 100 Bq/m<sup>3</sup> increase in the radon concentration. Radon gas levels vary by locality and the composition of the underlying soil and rocks. For example, in areas such as Cornwall in the UK (which has

granite as substrata), radon gas is a major problem, and buildings have to be force-ventilated with fans to lower radon gas concentrations. The United States Environmental Protection Agency (EPA) estimates that one in 15 homes in the U.S. has radon levels above the recommended guideline of 4 picocuries per liter (pCi/L) (148 Bq/m<sup>3</sup>). Iowa has the highest average radon concentration in the United States; studies performed there have demonstrated a 50% increased lung cancer risk, with prolonged radon exposure above the EPA's action level of 4 pCi/L.

## Asbestos



Ferruginous bodies the histopathologic finding associated with asbestosis

Asbestos can cause a variety of lung diseases, including lung cancer. There is a synergistic effect between tobacco smoking and asbestos in the formation of lung cancer. In the UK, asbestos accounts for 2–3% of male lung cancer deaths. Asbestos can also cause cancer of the pleura, called mesothelioma (which is different from lung cancer).

## Viruses

Viruses are known to cause lung cancer in animals, and recent evidence suggests similar potential in humans. Implicated viruses include human papillomavirus, JC virus, simian virus 40 (SV40), BK virus, and cytomegalovirus. These viruses may affect the cell cycle and inhibit apoptosis, allowing uncontrolled cell division.

## Particulate matter

Studies of the American Cancer Society cohort directly link the exposure to particulate matter with lung cancer. For example, if the concentration of particles in the air increases by only 1%, the risk of developing a lung cancer increases by 14%. Further, it has been established that particle size matters, as ultrafine particles penetrate further into the lungs.

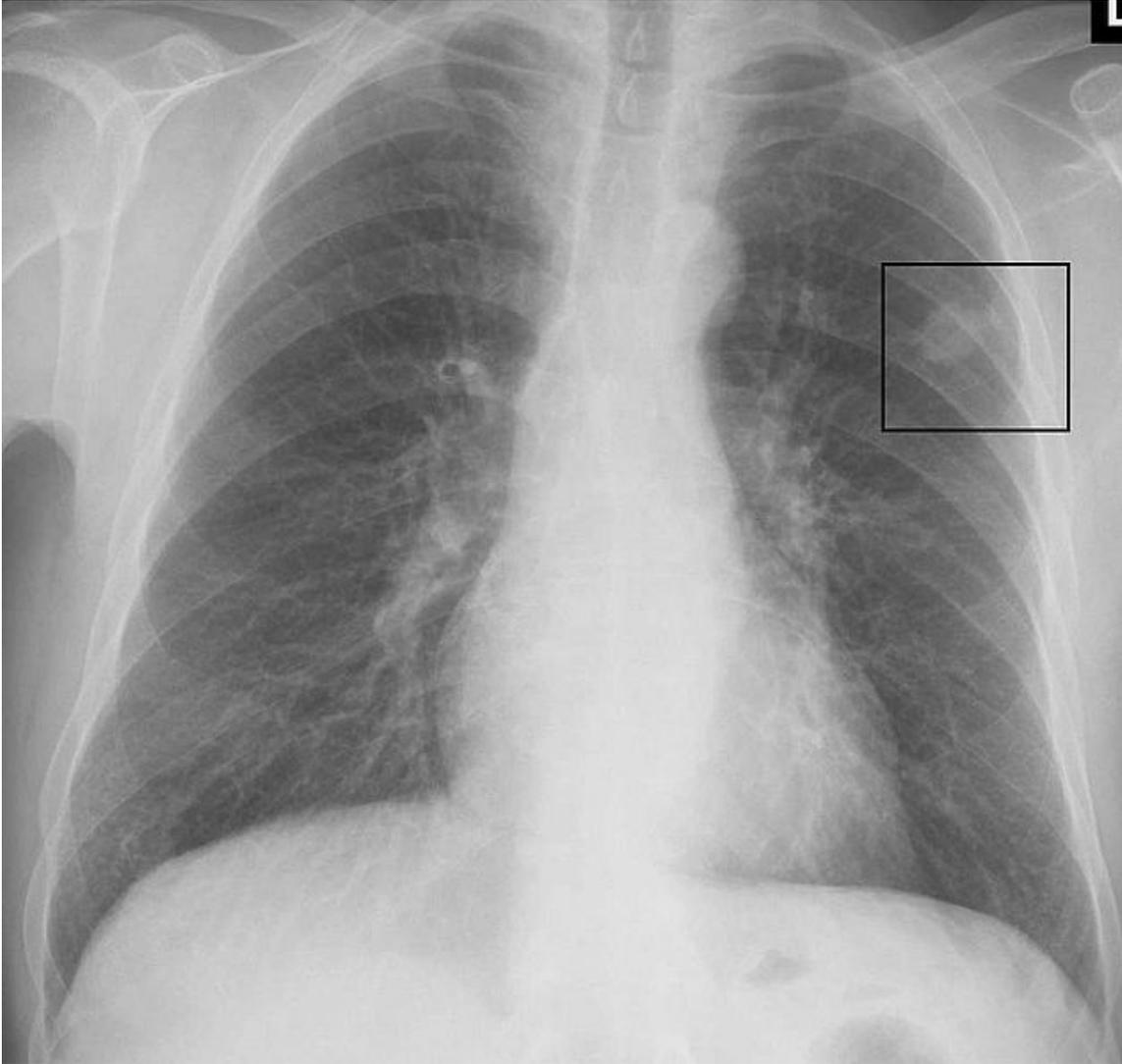
## Pathogenesis

Similar to many other cancers, lung cancer is initiated by activation of oncogenes or inactivation of tumor suppressor genes. Oncogenes are genes that are believed to make people more susceptible to cancer. Proto-oncogenes are believed to turn into oncogenes when exposed to particular carcinogens. Mutations in the *K-ras* proto-oncogene are responsible for 10–30% of lung adenocarcinomas. The epidermal growth factor receptor (EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion. Mutations and amplification of EGFR are common in non-small-cell lung cancer and provide the basis for treatment with EGFR-inhibitors. Her2/neu is affected less frequently. Chromosomal damage can lead to loss of heterozygosity. This can cause inactivation of tumor suppressor genes. Damage to chromosomes 3p, 5q, 13q, and 17p are particularly common in small-cell lung carcinoma. The *p53* tumor suppressor gene, located on chromosome 17p, is affected in 60-75% of cases. Other genes that are often mutated or amplified are *c-MET*, *NKX2-1*, *LKB1*, *PIK3CA*, and *BRAF*.

Several genetic polymorphisms are associated with lung cancer. These include polymorphisms in genes coding for interleukin-1, cytochrome P450, apoptosis promoters such as caspase-8, and DNA repair molecules such as XRCC1. People with these polymorphisms are more likely to develop lung cancer after exposure to carcinogens.

A recent study suggested that the MDM2 309G allele is a low-penetrant risk factor for developing lung cancer in Asians.

## **Diagnosis**



Chest radiograph showing a cancerous tumor in the left lung

Performing a chest radiograph is the first step if a patient reports symptoms that may suggest lung cancer. This may reveal an obvious mass, widening of the mediastinum (suggestive of spread to lymph nodes there), atelectasis (collapse), consolidation (pneumonia), or pleural effusion. If there are no radiographic findings but the suspicion is high (such as a heavy smoker with blood-stained sputum), bronchoscopy and/or a CT scan may provide the necessary information. Bronchoscopy or CT-guided biopsy is often used to identify the tumor type.

Abnormal findings in cells ("atypia") in sputum are associated with an increased risk of lung cancer. Sputum cytologic examination combined with other screening examinations may have a role in the early detection of lung cancer.



CT scan showing a cancerous tumor in the left lung

The differential diagnosis for patients who present with abnormalities on chest radiograph includes lung cancer as well as nonmalignant diseases. These include infectious causes such as tuberculosis or pneumonia, or inflammatory conditions such as sarcoidosis. These diseases can result in mediastinal lymphadenopathy or lung nodules, and sometimes mimic lung cancers. Lung cancer can also be an incidental finding: a solitary pulmonary nodule (also called a coin lesion) on a chest radiograph or CT scan taken for an unrelated reason. The definitive diagnosis of lung cancer and its classification (described above) is based on examination of the suspicious tissue under the microscope.

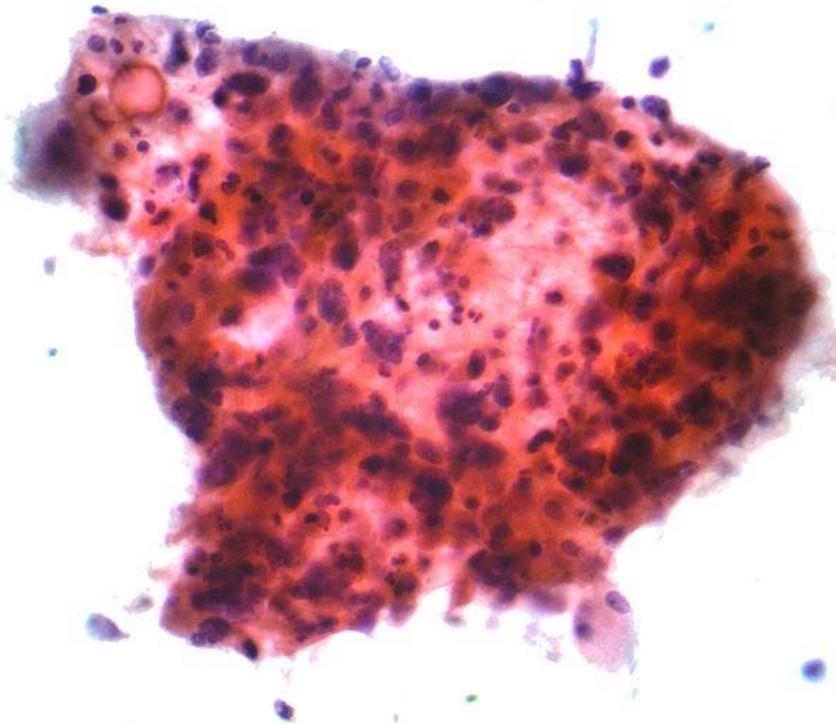
## Classification

Lung cancers are classified according to histological type. This classification has important implications for clinical management and prognosis of the disease. The vast majority of lung cancers are carcinomas—malignancies that arise from epithelial cells. The two most prevalent histological types of lung carcinoma, categorized by the size and appearance of the malignant cells seen by a histopathologist under a microscope: *non-small-cell* and *small-cell* lung carcinoma. The non-small-cell type is the most prevalent by far.

Frequency of histological types of lung cancer	
Histological type	Frequency (%)
Non-small-cell lung carcinoma	80.4
Small-cell lung carcinoma	16.8
Carcinoid	0.8
Sarcoma	0.1
Unspecified lung cancer	1.9

Cancer found outside of the lung may be determined to have arisen within the lung, as lung cancers that metastasize, i.e. spread, often retain a cell marker profile that allow a pathologist to say, with a good deal of certainty, that the tumor arose from the lung, i.e. is a *primary lung cancer*. Primary lung cancers of adenocarcinoma histology typically have nuclear immunostaining with TTF-1.

### Non-small-cell lung carcinoma



Micrograph of squamous carcinoma, a type of non-small-cell carcinoma. FNA specimen. Pap stain.

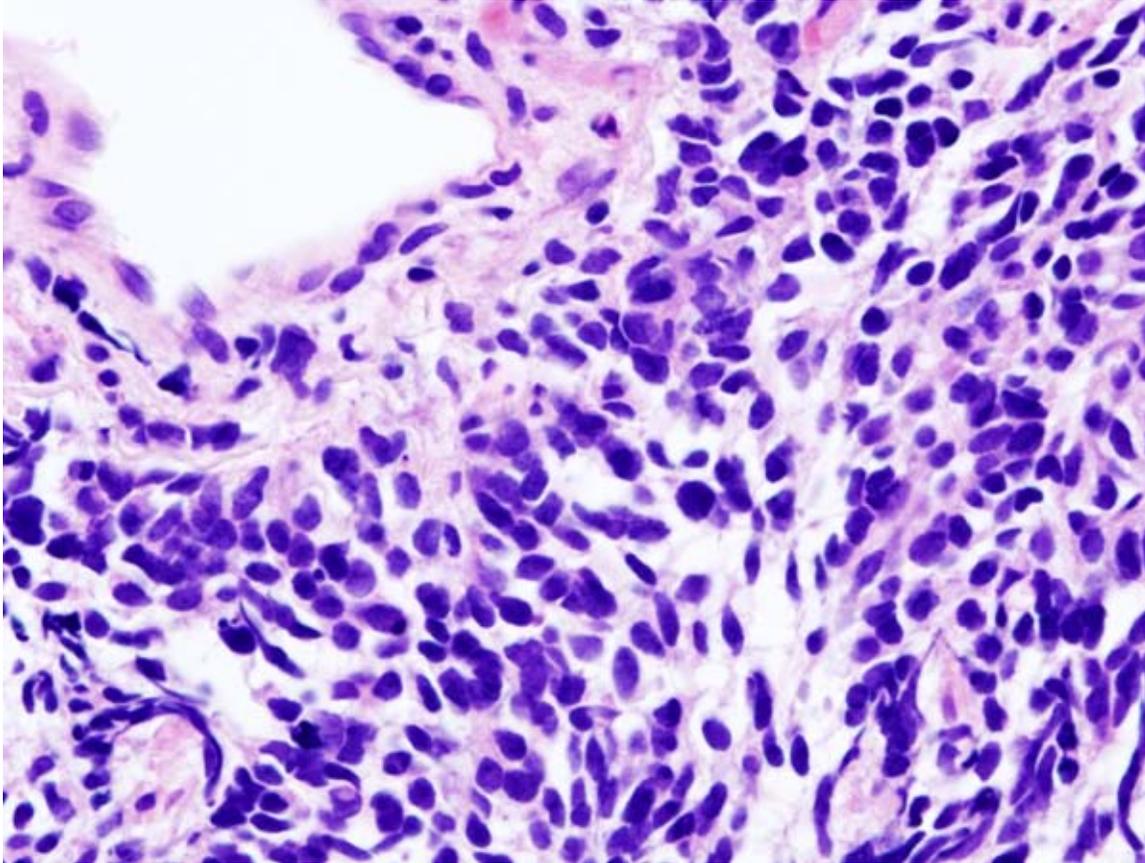
The non-small-cell lung carcinomas (NSCLC) are grouped together because their prognosis and management are similar. There are three main sub-types: squamous cell lung carcinoma, adenocarcinoma, and large-cell lung carcinoma.

<b>Sub-types of non-small-cell lung cancer in smokers and never-smokers</b>		
<b>Histological sub-type</b>	<b>Frequency of non-small-cell lung cancers (%)</b>	
	<b>Smokers</b>	<b>Never-smokers</b>
Squamous cell lung carcinoma	42	33
Adenocarcinoma (not otherwise specified)	39	35
Adenocarcinoma Bronchioloalveolar carcinoma	4	10
Carcinoid	7	16
Other	8	6

Accounting for 25% of lung cancers, squamous cell lung carcinoma usually starts near a central bronchus. A hollow cavity and associated necrosis are commonly found at the center of the tumor. Well-differentiated squamous cell lung cancers often grow more slowly than other cancer types.

Adenocarcinoma accounts for 40% of non-small-cell lung cancers. It usually originates in peripheral lung tissue. Most cases of adenocarcinoma are associated with smoking; however, among people who have never smoked ("never-smokers"), adenocarcinoma is the most common form of lung cancer. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have different responses to treatment.

## Small-cell lung carcinoma



Small-cell lung carcinoma (microscopic view of a core needle biopsy)

Small-cell lung carcinoma (SCLC) is less common. It was formerly referred to as "oat-cell" carcinoma. Most cases arise in the larger airways (primary and secondary bronchi) and grow rapidly, becoming quite large. The small cells contain dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association. While initially more sensitive to chemotherapy and radiation, it is often metastatic at presentation, and ultimately carries a worse prognosis. Small-cell lung cancers have long been dichotomously staged into limited and extensive stage disease. This type of lung cancer is strongly associated with smoking.

### Others

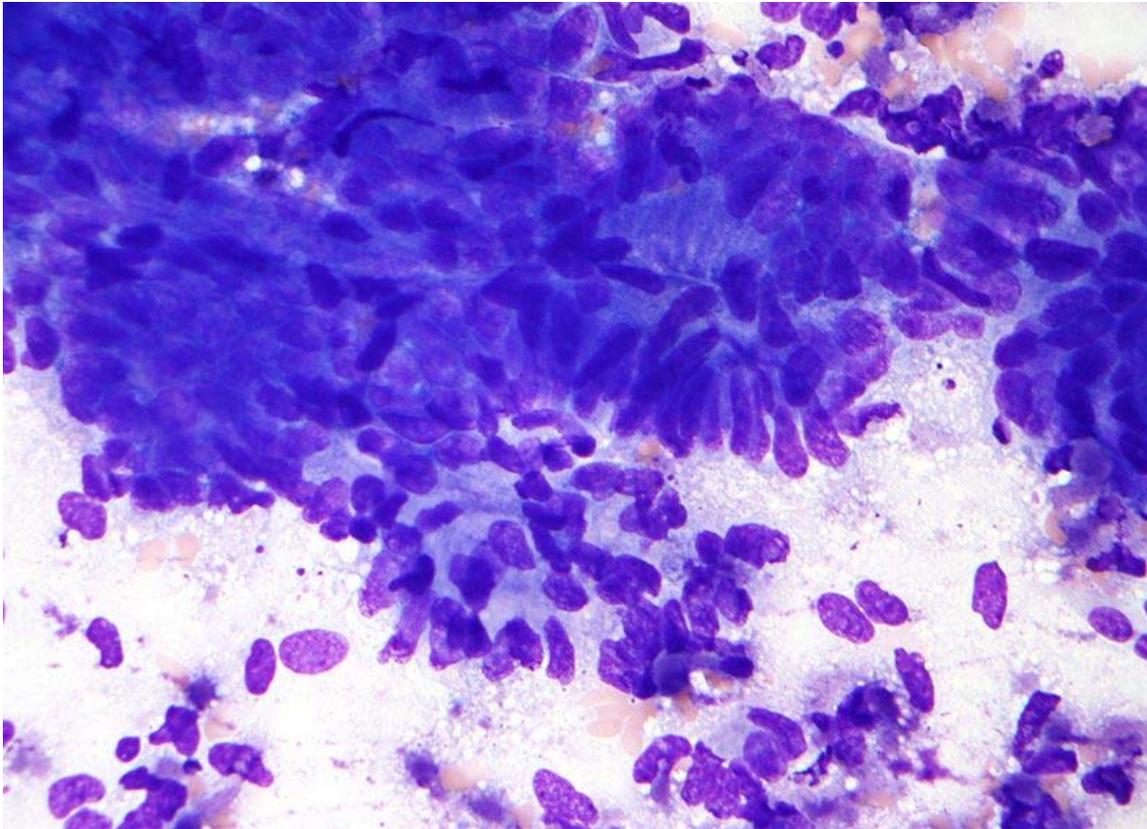
Lung cancers are highly heterogeneous malignancies, with tumors containing more than one subtype being very common.

Currently, the most widely recognized and utilized lung cancer classification system is the 4th revision of the Histological Typing of Lung and Pleural Tumours, published in 2004 as a cooperative effort by the World Health Organization and the International

Association for the Study of Lung Cancer. It recognizes numerous other distinct histopathological entities of non-small-cell lung carcinoma, organized into several additional subtypes, including sarcomatoid carcinoma, salivary gland tumors, carcinoid tumor, and adenosquamous carcinoma. The latter subtype includes tumors containing at least 10% each of adenocarcinoma and squamous cell carcinoma. When a tumor is found to contain a mixture of both small-cell carcinoma and non-small-cell carcinoma, it is classified as a variant of small-cell carcinoma and called a combined small-cell carcinoma. Combined small-cell carcinoma is the only currently recognized variant of small-cell carcinoma.

In infants and children, the most common primary lung cancers are pleuropulmonary blastoma and carcinoid tumor.

### **Metastasis**



Micrograph of a lung lymph node biopsy showing metastatic colorectal adenocarcinoma. Field stain.

The lung is a common place for metastasis of tumors from other parts of the body. Secondary cancers are classified by the site of origin; e.g., breast cancer that has spread to the lung is called *breast cancer*. Metastases often have a characteristic round appearance on chest radiograph. Solitary round lung nodules are not infrequently of an uncertain etiology and may prompt a lung biopsy.

In children, the majority of lung cancers are secondary.

Primary lung cancers themselves most commonly metastasize to the adrenal glands, liver, brain, and bone.

## **Staging**

Lung cancer staging is an assessment of the degree of spread of the cancer from its original source. It is an important factor affecting the prognosis and potential treatment of lung cancer. Non-small-cell lung carcinoma is staged from IA ("one A"; best prognosis) to IV ("four"; worst prognosis). Small-cell lung carcinoma is classified as *limited stage* if it is confined to one half of the chest and within the scope of a single radiotherapy field; otherwise, it is *extensive stage*.

## **Prevention**

Prevention is the most cost-effective means of fighting lung cancer. While in most countries industrial and domestic carcinogens have been identified and banned, tobacco smoking is still widespread. Eliminating tobacco smoking is a primary goal in the prevention of lung cancer, and smoking cessation is an important preventive tool in this process. Of utmost importance are prevention programs that target the young. In 1998 the Master Settlement Agreement entitled 46 states in the USA to an annual payout from the tobacco companies. Between the settlement money and tobacco taxes, each state's public health department funds their prevention programs, although none of the states are living up to the Center for Disease Control's recommended amount by spending 15 percent of tobacco taxes and settlement revenues on these prevention efforts.

Policy interventions to decrease passive smoking in public areas such as restaurants and workplaces have become more common in many Western countries, with California taking a lead in banning smoking in public establishments in 1998. Ireland played a similar role in Europe in 2004, followed by Italy and Norway in 2005, Scotland as well as several others in 2006, England in 2007, France in 2008 and Turkey in 2009. New Zealand has banned smoking in public places as of 2004. The state of Bhutan has had a complete smoking ban since 2005. In many countries, pressure groups are campaigning for similar bans. In 2007, Chandigarh became the first city in India to become smoke-free. India introduced a total ban on smoking at public places on Oct 2 2008.

Arguments cited against such bans are criminalisation of smoking, increased risk of smuggling, and the risk that such a ban cannot be enforced.

The long-term use of supplemental multivitamins—such as vitamin C, vitamin E, and folate—does not reduce the risk of lung cancer. Indeed long-term intake of high doses of vitamin E supplements may even increase the risk of lung cancer.

The World Health Organization has called for governments to institute a total ban on tobacco advertising to prevent young people from taking up smoking. They assess that such bans have reduced tobacco consumption by 16% where already instituted.

## **Screening**

Screening refers to the use of medical tests to detect disease in asymptomatic people. Possible screening tests for lung cancer include chest radiograph or computed tomography (CT). As of December 2009, screening programs for lung cancer have not demonstrated any benefit.

## **Treatment**

Treatment for lung cancer depends on the cancer's specific cell type, how far it has spread, and the patient's performance status. Common treatments include palliative care, surgery, chemotherapy, and radiation therapy.

## **Surgery**



Pneumonectomy specimen containing a squamous cell carcinoma, seen as a white area near the bronchi.

If investigations confirm lung cancer, CT scan and often positron emission tomography (PET) are used to determine whether the disease is localized and amenable to surgery or whether it has spread to the point where it cannot be cured surgically.

Blood tests and spirometry (lung function testing) are also necessary to assess whether the patient is well enough to be operated on. If spirometry reveals poor respiratory reserve (often due to chronic obstructive pulmonary disease), surgery may be contraindicated.

Surgery for lung cancer has an operative death rate of about 4.4%, depending on the patient's lung function and other risk factors. In non-small-cell lung carcinoma, surgery is usually only an option if the cancer is limited to one lung, up to stage IIIA. This is assessed with medical imaging (computed tomography, positron emission tomography). A sufficient preoperative respiratory reserve must be present to allow adequate lung function after the tissue is removed.

Procedures include wedge resection (removal of part of a lobe), segmentectomy (removal of an anatomic division of a particular lobe of the lung), lobectomy (one lobe), bilobectomy (two lobes), or pneumonectomy (whole lung). In patients with adequate respiratory reserve, lobectomy is the preferred option, as this minimizes the chance of local recurrence. If the patient does not have enough functional lung for this, wedge resection may be performed. Radioactive iodine brachytherapy at the margins of wedge excision may reduce recurrence to that of lobectomy.

Video-assisted thoracoscopic surgery and VATS lobectomy have allowed for minimally invasive approaches to lung cancer surgery that may have the advantages of quicker recovery, shorter hospital stay and diminished hospital costs.

Early studies suggested that small-cell lung carcinoma (SCLC) fared better when treated with chemotherapy and/or radiation than when treated surgically. While this approach to treating SCLC remains the current standard of care, the role of surgery in SCLC is being reconsidered, recent reviews indicating that surgery might improve outcomes when added to chemotherapy and radiation in early stage SCLC and combined forms of SCLC and NSCLC.

## **Radiotherapy**

Radiotherapy is often given together with chemotherapy, and may be used with curative intent in patients with non-small-cell lung carcinoma who are not eligible for surgery. This form of high intensity radiotherapy is called *radical radiotherapy*. A refinement of this technique is continuous hyperfractionated accelerated radiotherapy (CHART), in which a high dose of radiotherapy is given in a short time period. For small-cell lung carcinoma cases that are potentially curable, chest radiation is often recommended in addition to chemotherapy. The use of adjuvant thoracic radiotherapy following curative intent surgery for non-small-cell lung carcinoma is not well established and is

controversial. Benefits, if any, may only be limited to those in whom the tumor has spread to the mediastinal lymph nodes.

For both non-small-cell lung carcinoma and small-cell lung carcinoma patients, smaller doses of radiation to the chest may be used for symptom control (palliative radiotherapy). Unlike other treatments, it is possible to deliver palliative radiotherapy without confirming the histological diagnosis of lung cancer.

Brachytherapy (localized radiotherapy) may be given directly inside the airway when cancer affects a short section of bronchus. It is used when inoperable lung cancer causes blockage of a large airway.

Patients with limited-stage small-cell lung carcinoma are usually given prophylactic cranial irradiation (PCI). This is a type of radiotherapy to the brain, used to reduce the risk of metastasis. More recently, PCI has also been shown to be beneficial in those with extensive small-cell lung cancer. In patients whose cancer has improved following a course of chemotherapy, PCI has been shown to reduce the cumulative risk of brain metastases within one year from 40.4% to 14.6%.

Recent improvements in targeting and imaging have led to the development of extracranial stereotactic radiation in the treatment of early-stage lung cancer. In this form of radiation therapy, very high doses are delivered in a small number of sessions using stereotactic targeting techniques. Its use is primarily in patients who are not surgical candidates due to medical comorbidities.

## **Chemotherapy**

The chemotherapy regimen depends on the tumor type.

### **Small-cell lung carcinoma**

Even if relatively early stage, small-cell lung carcinoma is treated primarily with chemotherapy and radiation. In small-cell lung carcinoma, cisplatin and etoposide are most commonly used. Combinations with carboplatin, gemcitabine, paclitaxel, vinorelbine, topotecan, and irinotecan are also used. Celecoxib showed a potential signal of response in a small study.

### **Non-small-cell lung carcinoma**

Primary chemotherapy is also given in advanced and metastatic non-small-cell lung carcinoma.

Testing for the molecular genetic subtype of non-small-cell lung cancer may be of assistance in selecting the most appropriate initial therapy. For example, mutation of the epidermal growth factor receptor gene may predict whether initial treatment with a specific inhibitor or with chemotherapy is more advantageous.

Advanced non-small-cell lung carcinoma is often treated with cisplatin or carboplatin, in combination with gemcitabine, paclitaxel, docetaxel, etoposide, or vinorelbine. Bevacizumab improves results in non-squamous cancers treated with paclitaxel and carboplatin in patients less than 70 years old who have reasonable general performance status.

Pemetrexed has been studied extensively in non-small-cell lung cancer, with numerous studies since 1995. For adenocarcinoma and large-cell lung cancer, cisplatin with pemetrexed was more beneficial than cisplatin and gemcitabine; squamous cancer had the opposite results. As a consequence, subtyping of non-small lung cancer histology has become more important.

Bronchoalveolar carcinoma is a subtype of non-small-cell lung carcinoma that may respond to gefitinib and erlotinib.

### **Maintenance therapy**

In advanced non-small-cell lung cancer there are several approaches for continuing treatment after an initial response to therapy. Switch maintenance changes to different medications than the initial therapy and can use pemetrexed, erlotinib, and docetaxel, although pemetrexed is only used in non-squamous NSCLC.

### **Adjuvant chemotherapy**

Adjuvant chemotherapy refers to the use of chemotherapy after apparently curative surgery to improve the outcome. In non-small-cell lung cancer, samples are taken during surgery of nearby lymph nodes. If these samples contain cancer, the patient has stage II or III disease. In this situation, adjuvant chemotherapy may improve survival by up to 15%. Standard practice has often been to offer platinum-based chemotherapy (including either cisplatin or carboplatin). However, the benefit of platinum-based adjuvant chemotherapy was confined to patients who had tumors with low ERCC1 (excision repair cross-complementing 1) activity.

Adjuvant chemotherapy for patients with stage IB cancer is controversial, as clinical trials have not clearly demonstrated a survival benefit. Trials of preoperative chemotherapy (neoadjuvant chemotherapy) in resectable non-small-cell lung carcinoma have been inconclusive.

### **Interventional radiology**

Radiofrequency ablation should currently be considered an investigational technique in the treatment of bronchogenic carcinoma. It is done by inserting a small heat probe into the tumor to kill the tumor cells.

## **Palliative care**

In metastatic non–small-cell lung cancer the addition of palliative care to standard treatments improved the quality of life, lessened depression, lengthened life by 3 months, and decreased the use of aggressive care at the end of life.

Other studies in advanced cancer also found benefit from palliative care, or found hospice involvement to be beneficial. These approaches allow additional discussion of treatment options and provide opportunities to arrive at well-considered decisions and may avoid unhelpful but expensive care at the end of life.

However, palliative care may often be more appropriate in conjunction with chemotherapy at some point in the treatment of the cancer, rather than on its own. Over the past 20 years, the opposite question has also been asked: does chemotherapy add to supportive care? Superior survival has been repeatedly found in advanced non-small-cell lung cancer when study eligible recipients receive appropriate chemotherapy rather than supportive care alone. For example, 1994 recommendations based on reports that combined the results of several available studies found an increase in average survival from 3.9 months for best supportive care alone to 6.7 months with the addition of chemotherapy, as well as an improved quality of life. A systematic review from Sweden in 2001 looked at numerous chemotherapy reports over many years in lung cancer with adequate physical fitness. Compared to supportive care alone there was a 1.5 to 3 months prolongation of survival with chemotherapy in general, with better results seen with what were then newer agents. Symptomatic relief and an improvement in quality of life were also evident. A contemporaneous independent British review was consistent with this conclusion.

Despite a change in population demographics, this continues to hold up. A 2008 update by the NSCLC Meta-Analyses Collaborative Group looked at individual patient data from clinical trials subsequent to 1995, and recommended that chemotherapy should be considered in advanced non-small-cell lung cancer provided the recipient wanted treatment and was adequately fit to be able to tolerate it. This analysis was the basis of a 2010 Cochrane Review reporting that chemotherapy improves overall survival in advanced non-small-cell lung cancer, and finding a benefit in different subtypes of the cancer.

Palliative care is an essential and routine component of evidence-based, high-quality care for the management of advanced lung cancer but it is also clear that the best way to deliver palliative care is unknown. By way of emphasis, an analysis of almost 400 randomized controlled trials of palliative care concluded that the evidence for specialized palliative care as a specific intervention is limited, due to methodological shortcomings of the data. That review found that the most consistent benefit of palliative care was a increased perception by family members of good quality care. Which specific components of palliative care are of benefit is unknown, warranting further clinical assessment of different palliative approaches.

## **Prognosis**

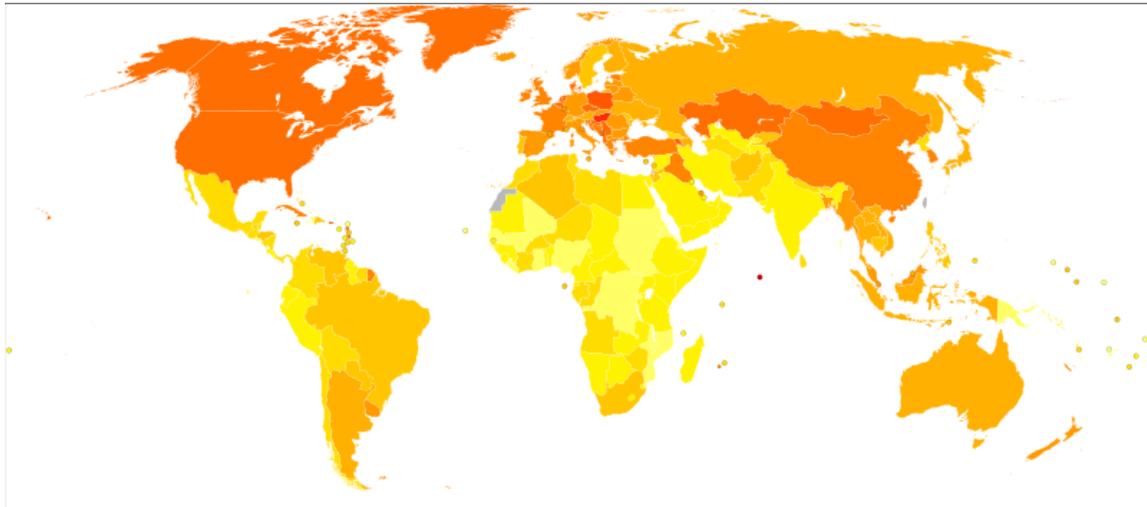
Prognostic factors in non-small-cell lung cancer include presence or absence of pulmonary symptoms, tumor size, cell type (histology), degree of spread (stage) and metastases to multiple lymph nodes, and vascular invasion. For patients with inoperable disease, prognosis is adversely affected by poor performance status and weight loss of more than 10%. Prognostic factors in small-cell lung cancer include performance status, gender, stage of disease, and involvement of the central nervous system or liver at the time of diagnosis.

For non-small-cell lung carcinoma (NSCLC), prognosis is generally poor. Following complete surgical resection of stage IA disease, five-year survival is 67%. With stage IB disease, five-year survival is 57%. The five-year survival rate of patients with stage IV NSCLC is about 1%.

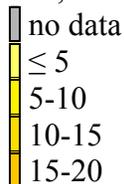
For small-cell lung carcinoma, prognosis is also generally poor. The overall five-year survival for patients with SCLC is about 5%. Patients with extensive-stage SCLC have an average five-year survival rate of less than 1%. The median survival time for limited-stage disease is 20 months, with a five-year survival rate of 20%.

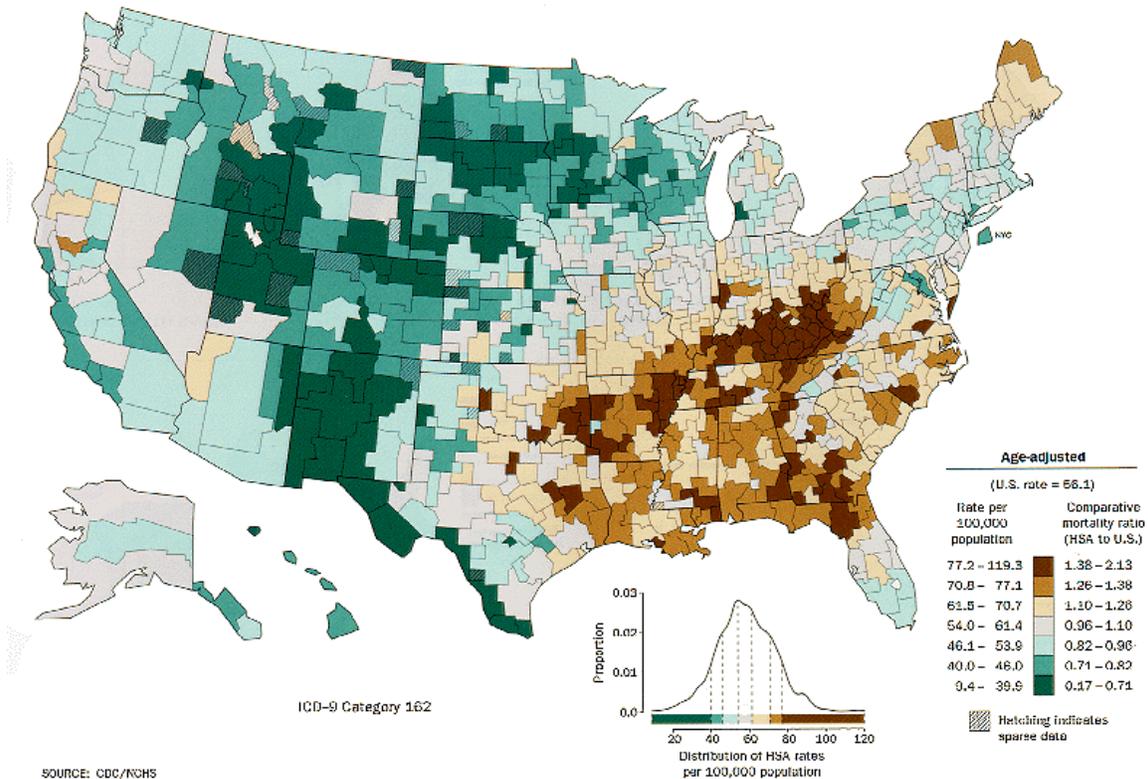
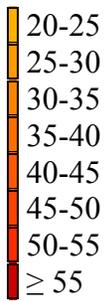
According to data provided by the National Cancer Institute, the median age at diagnosis of lung cancer in the United States is 70 years, and the median age at death is 72 years.

## **Epidemiology**



Age-standardized death from tracheal, bronchial, and lung cancers per 100,000 inhabitants in 2004.





### Lung cancer distribution in the United States

Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality (1.1 million new cases per year and 0.95 million deaths in males and 0.51 million new cases per year and 0.43 million deaths in females). The highest rates are in Europe and North America. The population segment most likely to develop lung cancer is over-fifties who have a history of smoking. Lung cancer is the second most commonly occurring form of cancer in most Western countries, and it is the leading cancer-related cause of death. In contrast to the mortality rate in men, which began declining more than 20 years ago, women's lung cancer mortality rates have been rising for over the last decades, and are just recently beginning to stabilize. The evolution of "Big Tobacco" plays a significant role in the smoking culture. Tobacco companies have focused their efforts since the 1970s at marketing their product toward women and girls, especially with "light" and "low-tar" cigarettes. Among lifetime nonsmokers, men have higher age-standardized lung cancer death rates than women.

Not all cases of lung cancer are due to smoking, but the role of passive smoking is increasingly being recognized as a risk factor for lung cancer—leading to policy interventions to decrease undesired exposure of nonsmokers to others' tobacco smoke. Emissions from automobiles, factories, and power plants also pose potential risks.

Eastern Europe has the highest lung cancer mortality among men, while northern Europe and the U.S. have the highest mortality among women. In the United States, black men and women have a higher incidence. Lung cancer incidence is currently less common in developing countries. With increased smoking in developing countries, the incidence is expected to increase in the next few years, notably in China and India.

Lung cancer incidence (by country) has an inverse correlation with sunlight and UVB exposure. One possible explanation is a preventive effect of vitamin D (which is produced in the skin on exposure to sunlight).

From the 1950s, the incidence of lung adenocarcinoma started to rise relative to other types of lung cancer. This is partly due to the introduction of filter cigarettes. The use of filters removes larger particles from tobacco smoke, thus reducing deposition in larger airways. However the smoker has to inhale more deeply to receive the same amount of nicotine, increasing particle deposition in small airways where adenocarcinoma tends to arise. The incidence of lung adenocarcinoma in the U.S. has fallen since 1999. This may be due to reduction in environmental air pollution. However, in some developing countries like India, there has been little change in the epidemiology with squamous cell carcinoma continuing to be the predominant histological type. An absence of change in the type of tobacco smoking or the pattern of tobacco consumption in the population could be one of the possible reasons.

## ***History***

Lung cancer was uncommon before the advent of cigarette smoking; it was not even recognized as a distinct disease until 1761. Different aspects of lung cancer were described further in 1810. Malignant lung tumors made up only 1% of all cancers seen at autopsy in 1878, but had risen to 10–15% by the early 1900s. Case reports in the medical literature numbered only 374 worldwide in 1912, but a review of autopsies showed that the incidence of lung cancer had increased from 0.3% in 1852 to 5.66% in 1952. In Germany in 1929, physician Fritz Lickint recognized the link between smoking and lung cancer, which led to an aggressive antismoking campaign. The British Doctors Study, published in the 1950s, was the first solid epidemiological evidence of the link between lung cancer and smoking. As a result, in 1964 the Surgeon General of the United States recommended that smokers should stop smoking.

The connection with radon gas was first recognized among miners in the Ore Mountains near Schneeberg, Saxony. Silver has been mined there since 1470, and these mines are rich in uranium, with its accompanying radium and radon gas. Miners developed a disproportionate amount of lung disease, eventually recognized as lung cancer in the

1870s. An estimated 75% of former miners died from lung cancer. Despite this discovery, mining continued into the 1950s, due to the USSR's demand for uranium.

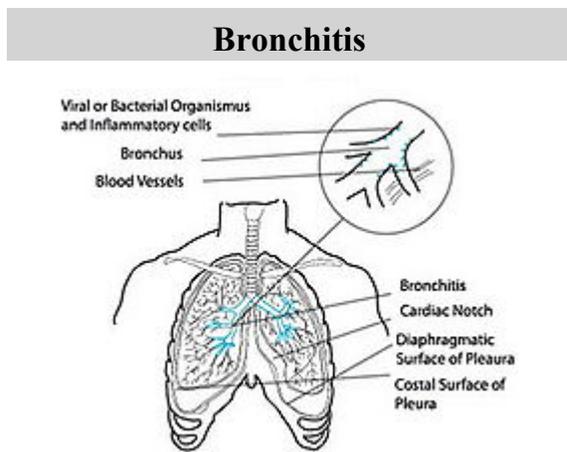
The first successful pneumonectomy for lung cancer was performed in 1933. Palliative radiotherapy has been used since the 1940s. Radical radiotherapy, initially used in the 1950s, was an attempt to use larger radiation doses in patients with relatively early stage lung cancer but who were otherwise unfit for surgery. In 1997, continuous hyperfractionated accelerated radiotherapy (CHART) was seen as an improvement over conventional radical radiotherapy.

With small-cell lung carcinoma, initial attempts in the 1960s at surgical resection and radical radiotherapy were unsuccessful. In the 1970s, successful chemotherapy regimens were developed.

## Chapter 15

# Bronchitis and Acute Bronchitis

## Bronchitis



This diagram shows acute bronchitis.

**ICD-10** J20.-J21., J42.

**ICD-9** 466, 491

**DiseasesDB** 29135

**MedlinePlus** 001087

**eMedicine** [article/807035](#) [article/297108](#)

**MeSH** D001991

**Bronchitis** is inflammation of the mucous membranes of the bronchi, the airways that carry airflow from the trachea into the lungs. Bronchitis can be divided into two categories, acute and chronic, each of which has unique etiologies, pathologies, and therapies.

Acute bronchitis is characterized by the development of a cough, with or without the production of sputum, mucus that is expectorated (coughed up) from the respiratory tract.

Acute bronchitis often occurs during the course of an acute viral illness such as the common cold or influenza. Viruses cause about 90% of cases of acute bronchitis, whereas bacteria account for less than 10%.

Chronic bronchitis, a type of chronic obstructive pulmonary disease, is characterized by the presence of a productive cough that lasts for 3 months or more per year for at least 2 years. Chronic bronchitis most often develops due to recurrent injury to the airways caused by inhaled irritants. Cigarette smoking is the most common cause, followed by air pollution and occupational exposure to irritants.

## **Chronic bronchitis**

Chronic bronchitis, a type of chronic obstructive pulmonary disease, is defined by a productive cough that lasts for 3 months or more per year for at least 2 years. Other symptoms may include wheezing and shortness of breath, especially upon exertion. The cough is often worse soon after awakening, and the sputum produced may have a yellow or green color and may be streaked with blood.

Chronic bronchitis is caused by recurring injury or irritation to the respiratory epithelium of the bronchi, resulting in chronic inflammation, edema (swelling), and increased production of mucus by goblet cells. Airflow into and out of the lungs is partly blocked because of the swelling and extra mucus in the bronchi or due to reversible bronchospasm.

Most cases of chronic bronchitis are caused by smoking cigarettes or other forms of tobacco. Chronic inhalation of irritating fumes or dust from occupational exposure or air pollution may also be causative. About 5% of the population has chronic bronchitis, and it is two times more common in males than females.

Chronic bronchitis is treated symptomatically. Inflammation and edema of the respiratory epithelium may be reduced with inhaled corticosteroids. Wheezing and shortness of breath can be treated by reducing bronchospasm (reversible narrowing of smaller bronchi due to constriction of the smooth muscle) with bronchodilators such as inhaled  $\beta$ -Adrenergic agonists (e.g., salbutamol) and inhaled anticholinergics (e.g., ipratropium bromide). Hypoxemia, too little oxygen in the blood, can be treated with supplemental oxygen. However, oxygen supplementation can result in decreased respiratory drive, leading to increased blood levels of carbon dioxide and subsequent respiratory acidosis.

The most effective method of preventing chronic bronchitis and other forms of COPD is to avoid smoking cigarettes and other forms of tobacco.

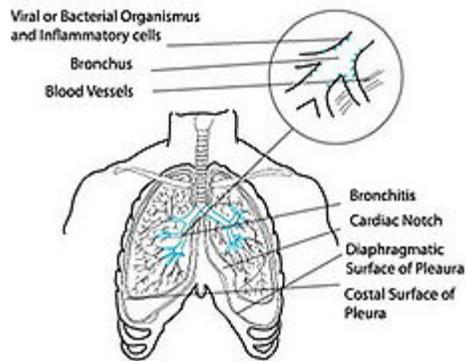
On pulmonary tests, a bronchitic (bronchitis) may present a decreased FEV1 and FEV1/FVC. However, unlike the other common obstructive disorders, asthma and emphysema, bronchitis rarely causes a high residual volume. This is because the air flow obstruction found in bronchitis is due to increased resistance, which, in general, does not cause the airways to collapse prematurely and trap air in the lungs.

## Protracted bacterial bronchitis

Protracted bacterial bronchitis is defined as a chronic wet cough, with a positive bronchoalveolar lavage (BAL), that resolves with antibiotics. It is usually caused by streptococcus pneumoniae, haemophilus influenzae, or moraxella catarrhalis.

## Acute bronchitis

### Acute bronchitis



This image shows the consequences of acute bronchitis.

**ICD-10** J20.-J21.

**ICD-9** 466

**MeSH** D001991

**Acute bronchitis** is an inflammation of the large bronchi (medium-size airways) in the lungs that is usually caused by viruses or bacteria and may last several days or weeks. Characteristic symptoms include cough, sputum (phlegm) production, and shortness of breath and wheezing related to the obstruction of the inflamed airways. Diagnosis is by clinical examination and sometimes microbiological examination of the phlegm. Treatment for acute bronchitis is typically symptomatic. As viruses cause most cases of acute bronchitis, antibiotics should not be used unless microscopic examination of gram-stained sputum reveals large numbers of bacteria.

### **Cause/etiology**

Acute bronchitis can be caused by contagious pathogens. In about half of instances of acute bronchitis, a bacterial or viral pathogen is identified. Typical viruses include respiratory syncytial virus, rhinovirus, influenza, and others.

- Damage caused by irritation of the airways leads to inflammation and leads to neutrophils infiltrating the lung tissue.
- Mucosal hypersecretion is promoted by a substance released by neutrophils.
- Further obstruction to the airways is caused by more goblet cells in the small airways. This is typical of chronic bronchitis.
- Although infection is not the reason or cause of chronic bronchitis, it is seen to aid in sustaining the bronchitis.

## ***Signs and symptoms***

Bronchitis may be indicated by an expectorating cough, shortness of breath (dyspnea), and wheezing. On occasion, chest pains, fever, and fatigue or malaise may also occur. In addition, bronchitis caused by Adenoviridae may cause systemic and gastrointestinal symptoms as well. However, the coughs due to bronchitis can continue for up to three weeks or more even after all other symptoms have subsided.

## ***Diagnosis***

A physical examination will often reveal decreased intensity of breath sounds, wheezing, rhonchi, and prolonged expiration. Most doctors rely on the presence of a persistent dry or wet cough as evidence of bronchitis.

A variety of tests may be performed in patients presenting with cough and shortness of breath:

- A chest X-ray that reveals hyperinflation; collapse and consolidation of lung areas would support a diagnosis of pneumonia. Some conditions that predispose to bronchitis may be indicated by chest radiography.
- A sputum sample showing neutrophil granulocytes (inflammatory white blood cells) and culture showing that has pathogenic microorganisms such as *Streptococcus* species
- A blood test would indicate inflammation (as indicated by a raised white blood cell count and elevated C-reactive protein).

## ***Treatment***

### **Antibiotics**

Only about 5-10% of bronchitis cases are caused by a bacterial infection. Most cases of bronchitis are caused by a viral infection and are "self-limited" and resolve themselves in a few weeks. Acute bronchitis should not be treated with antibiotics unless microscopic examination of the sputum reveals large numbers of bacteria. Treating non-bacterial illnesses with antibiotics leads to the promotion of antibiotic-resistant bacteria, which increase morbidity and mortality.

## **Smoking cessation**

Many physicians recommend that, to help the bronchial tree heal faster and not make bronchitis worse, smokers should quit smoking completely in order to allow their lungs to recover from the layer of tar that builds up over time.

## **Antihistamines**

Using over-the-counter antihistamines may be harmful in the self-treatment of bronchitis.

An effect of antihistamines is to thicken mucus secretions. Expelling infected mucus via coughing can be beneficial in recovering from bronchitis. Expulsion of the mucus may be hindered if it is thickened. Antihistamines can help bacteria to persist and multiply in the lungs by increasing its residence time in a warm, moist environment of thickened mucus.

Using antihistamines along with an expectorant cough syrup may be doubly harmful, encouraging the production of mucus and then thickening that which is produced. Using an expectorant cough syrup alone might be useful in flushing bacteria from the lungs. Using an antihistamine along with it works against the intention of using the expectorant.

## ***Prognosis***

Acute bronchitis usually lasts a few days or weeks. It may accompany or closely follow a cold or the flu, or may occur on its own. Bronchitis usually begins with a dry cough, including waking the sufferer at night. After a few days, it progresses to a wetter or productive cough, which may be accompanied by fever, fatigue, and headache. The fever, fatigue, and malaise may last only a few days; but the wet cough may last up to several weeks.

Should the cough last longer than a month, some doctors may issue a referral to an otorhinolaryngologist (ear, nose and throat doctor) to see if a condition other than bronchitis is causing the irritation. It is possible that having irritated bronchial tubes for as long as a few months may inspire asthmatic conditions in some patients.

In addition, if one starts coughing mucus tinged with blood, one should see a doctor. In rare cases, doctors may conduct tests to see whether the cause is a serious condition such as tuberculosis or lung cancer.

## ***Prevention***

In 1985, University of Newcastle, Australia Professor Robert Clancy developed an oral vaccine for acute bronchitis. This vaccine was commercialised four years later.

## Chapter 16

# Emphysema

### Emphysema



A lateral chest x-ray of a person with emphysema.

Note the barrel chest and flat diaphragm.

<b>ICD-10</b>	J43.
<b>ICD-9</b>	492
<b>DiseasesDB</b>	4190
<b>MedlinePlus</b>	000136
<b>eMedicine</b>	med/654
<b>MeSH</b>	D011656

**Emphysema** is a long-term, progressive disease of the lungs that primarily causes shortness of breath. In people with emphysema, the tissues necessary to support the physical shape and function of the lungs are destroyed. It is included in a group of diseases called chronic obstructive pulmonary disease or COPD (pulmonary refers to the

lungs). Emphysema is called an obstructive lung disease because the destruction of lung tissue around smaller sacs, called alveoli, makes these air sacs unable to hold their functional shape upon exhalation. It is often caused by smoking or long-term exposure to air pollution.

The term means *swelling* and comes from the Greek ἔμφυσᾶν *emhysan* meaning *inflate*, itself composed of ἐν *en* meaning *in* and φυσᾶν *physan* meaning *breath, blast*.

## **Classification**

Emphysema can be classified into primary and secondary. However, it is more commonly classified by location into panacinar and centroacinar (or panacinar and centriacinar, or centrilobular and panlobular).

- *Panacinar* (or *panlobular*) emphysema: The entire respiratory acinus, from respiratory bronchiole to alveoli, is expanded. Occurs more commonly in the lower lobes, especially basal segments, and anterior margins of the lungs.
- *Centriacinar* (or *centrilobular*) emphysema: The respiratory bronchiole (proximal and central part of the acinus) is expanded. The distal acinus or alveoli are unchanged. Occurs more commonly in the upper lobes.

Other types include distal acinar and irregular. A special type is *congenital lobar emphysema (CLE)*.

## **Congenital lobar emphysema**

CLE results in overexpansion of a pulmonary lobe and resultant compression of the remaining lobes of the ipsilateral lung, and possibly also the contralateral lung. There is bronchial narrowing because of weakened or absent bronchial cartilage. There may be congenital extrinsic compression, commonly by an abnormally large pulmonary artery. This causes malformation of bronchial cartilage, making them soft and collapsible. CLE is potentially reversible, yet possibly life-threatening, causing respiratory distress in the neonate.

## **Paraseptal emphysema**

Paraseptal emphysema is a type of emphysema which involves the alveolar ducts and sacs at the lung periphery. The emphysematous areas are subpleural in location and often surrounded by interlobular septa (hence the name). It may be an incidental finding in young adults, and may be associated with spontaneous pneumothorax. It may also be seen in older patients with centrilobular emphysema. Both centrilobular and paraseptal emphysema may progress to bullous emphysema. A bulla is defined as being at least 1cm in diameter, and with a wall less than 1mm thick. Bullae are thought to arise by air trapping in emphysematous spaces, causing local expansion.

## ***Signs and symptoms***

Emphysema is a disease of the lung tissue caused by destruction of structures feeding the alveoli, in some cases owing to the action of alpha 1-antitrypsin deficiency. Smoking is one major cause of this destruction, which causes the small airways in the lungs to collapse during forced exhalation. As a result, airflow is impeded and air becomes trapped, just as in other obstructive lung diseases. Symptoms include shortness of breath on exertion, and an expanded chest.

People with this disease do not get enough oxygen and cannot remove carbon dioxide from their blood; they therefore exhibit dyspnea (shortness of breath). At first this occurs only during physical activity. Eventually it will occur after any physical exertion. Later the patient may be dyspneic all the time, even when relaxing. Because breathing is difficult, the patient must use accessory muscles to help them breathe; tachypnea (rapid breathing) may occur they try to extend their exertion. They may have trouble coughing and lowered amounts of sputum. They may also lose weight.

The anteroposterior diameter of their chest may increase; this symptom is sometimes referred as "barrel chest." The patient may lean forward with arms extended or resting on something to help them breathe.

When lung auscultation and chest percussion is performed a hyperresonant sound is heard (Mc Cance). The patient may exhibit symptoms of cyanosis, lowered oxygen levels and increased carbon dioxide levels.

## ***Causes***

The majority of all emphysema cases are caused by smoking tobacco. Emphysema cases that are caused by other etiologies are referred to as secondary emphysema.

In some cases it may be due to alpha 1-antitrypsin deficiency. Severe cases of A1AD may also develop cirrhosis of the liver, where the accumulated A1AT leads to a fibrotic reaction.

Some types of emphysema are considered a normal part of aging and are found in the elderly whose lungs have deteriorated due to age. At about 20 years of age, people stop developing new alveoli tissue. In the years following the cessation of the development of new alveoli, lung tissue can start to deteriorate. This is a normal, natural part of aging in healthy people. Alveoli will die, the number of lung capillaries will decline and the elastin of the lungs will begin to break down causing a loss of pulmonary elasticity. As people age, they will also lose strength and mass in their chest muscles causing these muscles to become weaker. In addition, bones can start to deteriorate and a person's posture can change. Together, all of these age-related manifestations can cause the development of emphysema. Though not all elderly people will develop emphysema, they are all at risk of having decreased respiratory function.

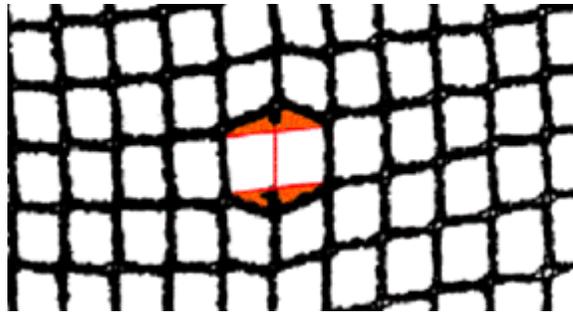
Other causes of emphysema can be anything that causes the body to be unable to inhibit proteolytic enzymes in the lung. This could be exposure to air pollution, second hand smoke or other chemicals and toxins.

### ***Pathophysiology***



Pathology of lung showing centrilobular emphysema characteristic of smoking. Closeup of fixed, cut surface shows multiple cavities lined by heavy black carbon deposits. (CDC/Dr. Edwin P. Ewing, Jr., 1973)

In normal breathing, air is drawn in through the bronchi and into the alveoli, which are tiny sacs surrounded by capillaries. Alveoli absorb oxygen and then transfer it into the blood. When toxicants, such as cigarette smoke, are breathed into the lungs, the harmful particles become trapped in the alveoli, causing a localized inflammatory response. Chemicals released during the inflammatory response (e.g., elastase) can eventually cause the alveolar septum to disintegrate. This condition, known as septal rupture, leads to significant deformation of the lung architecture. The key mechanical event consequent to septal rupture is that the resulting cavity is larger than the sum of the two alveolar spaces;



An elastic net distended on finite surface may offer a bidimensional model useful for understanding the pure mechanical consequences of septal rupture. In red is the extra space of the new cavity after septal rupture due to the lung elastic recoil at the expenses of the surrounding healthy meshes (alveoli)

in fact because of the lacking mechanical support of the broken septa the lung elastic recoil further enlarges this new space, necessarily at the expenses of the surrounding healthy parenchyma. In other words, as immediate and spontaneous consequence of septal rupture, the elastic lung recoil resets healthy parenchyma expansion at a lower level, in proportion to the amount of septal disruption.

The large cavities left by the septal rupture are known as **bullae (sin. = bulla)**. These deformations result in a large decrease of alveoli surface area used for gas exchange, as well as decreased ventilation of the surrounding healthy parenchyma. This results in a decreased Transfer Factor of the Lung for Carbon Monoxide (TLCO). To accommodate the decreased surface area, thoracic cage expansion (barrel chest) and diaphragm contraction (flattening) take place. Expiration, which physiologically depends completely on lung elastic recoil, increasingly depends on the thoracic cage and abdominal muscle action, particularly in the end expiratory phase. Due to decreased ventilation, the ability to exude carbon dioxide is significantly impaired. In the more serious cases, oxygen uptake is also impaired. As the alveoli continue to break down, hyperventilation is unable to compensate for the progressively shrinking surface area, and the body is not able to maintain high enough oxygen levels in the blood. The body's last resort is vasoconstricting appropriate vessels. This leads to pulmonary hypertension, which places increased strain on the right side of the heart, the side responsible for pumping deoxygenated blood to the lungs. The heart muscle thickens in order to pump more blood. This condition is often accompanied by the appearance of jugular venous distension. Eventually, as the heart continues to fail, it becomes larger and blood backs up in the liver.

Patients with alpha 1-antitrypsin deficiency (A1AD) are more likely to suffer from emphysema. A1AT inhibits inflammatory enzymes (such as elastase) from destroying the alveolar tissue. Most A1AD patients do not develop clinically significant emphysema, but smoking and severely decreased A1AT levels (10-15%) can cause emphysema at a young age. The type of emphysema caused by A1AD is known as *panacinar* emphysema (involving the entire acinus) as opposed to *centrilobular* emphysema, which is caused by smoking. Panacinar emphysema typically affects the lower lungs, while centrilobular

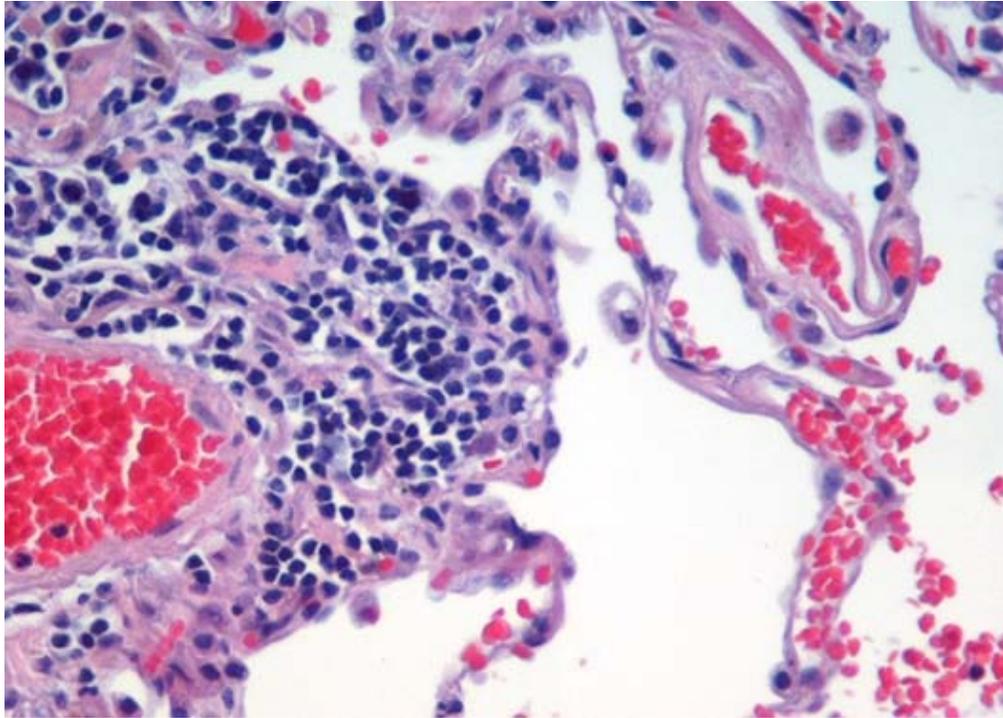
emphysema affects the upper lungs. A1AD causes about 2% of all emphysema. Smokers with A1AD are at the greatest risk for emphysema. Mild emphysema can often develop into a severe case over a short period of time (1–2 weeks).

While A1AD provides some insight into the pathogenesis of the disease, hereditary A1AT deficiency only accounts for a small proportion of the disease. Studies for the better part of the past century have focused mainly upon the putative role of leukocyte elastase (also *neutrophil elastase*), a serine protease found in neutrophils, as a primary contributor to the connective tissue damage seen in the disease. This hypothesis, a result of the observation that neutrophil elastase is the primary substrate for A1AT, and A1AT is the primary inhibitor of neutrophil elastase, together have been known as the "*protease-antiprotease*" theory, implicating neutrophils as an important mediator of the disease. However, more recent studies have brought into light the possibility that one of the many other numerous proteases, especially matrix metalloproteases might be equally or more relevant than neutrophil elastase in the development of non-hereditary emphysema.

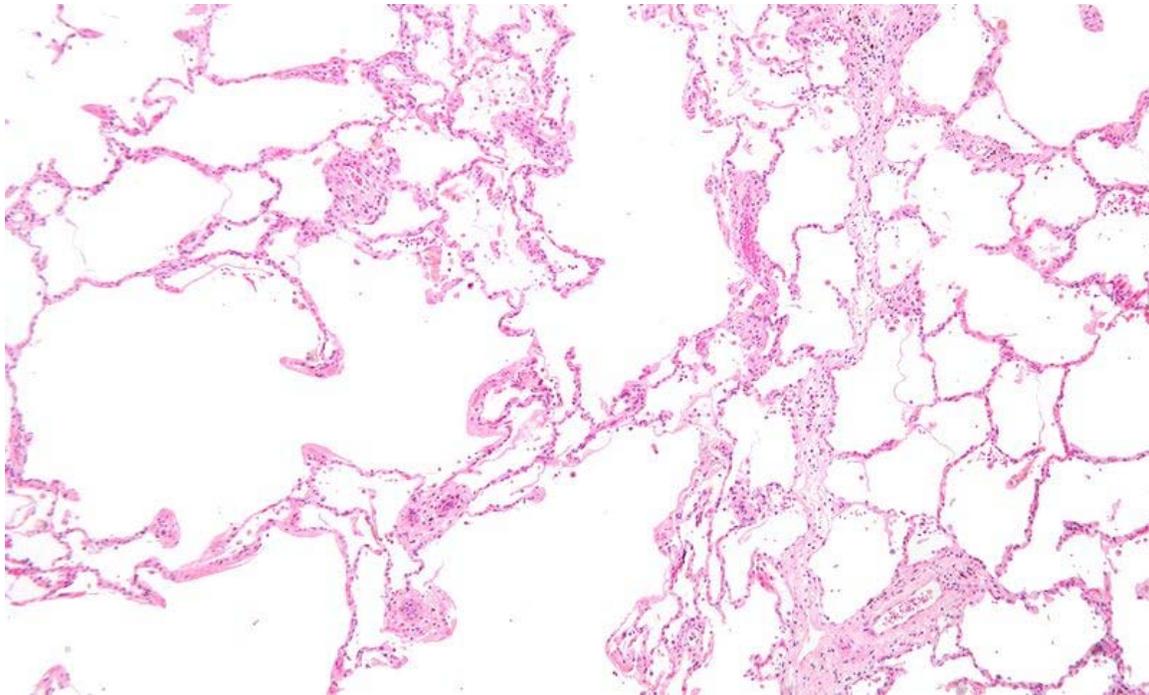
The better part of the past few decades of research into the pathogenesis of emphysema involved animal experiments where various proteases were instilled into the trachea of various species of animals. These animals developed connective tissue damage, which was taken as support for the protease-antiprotease theory. However, just because these substances can destroy connective tissue in the lung, as anyone would be able to predict, doesn't establish causality. More recent experiments have focused on more technologically advanced approaches, such as ones involving genetic manipulation. One particular development with respect to our understanding of the disease involves the production of protease "knock-out" animals, which are genetically deficient in one or more proteases, and the assessment of whether they would be less susceptible to the development of the disease. Often individuals who are unfortunate enough to contract this disease have a very short life expectancy, often 0–3 years at most.

## **Diagnosis**

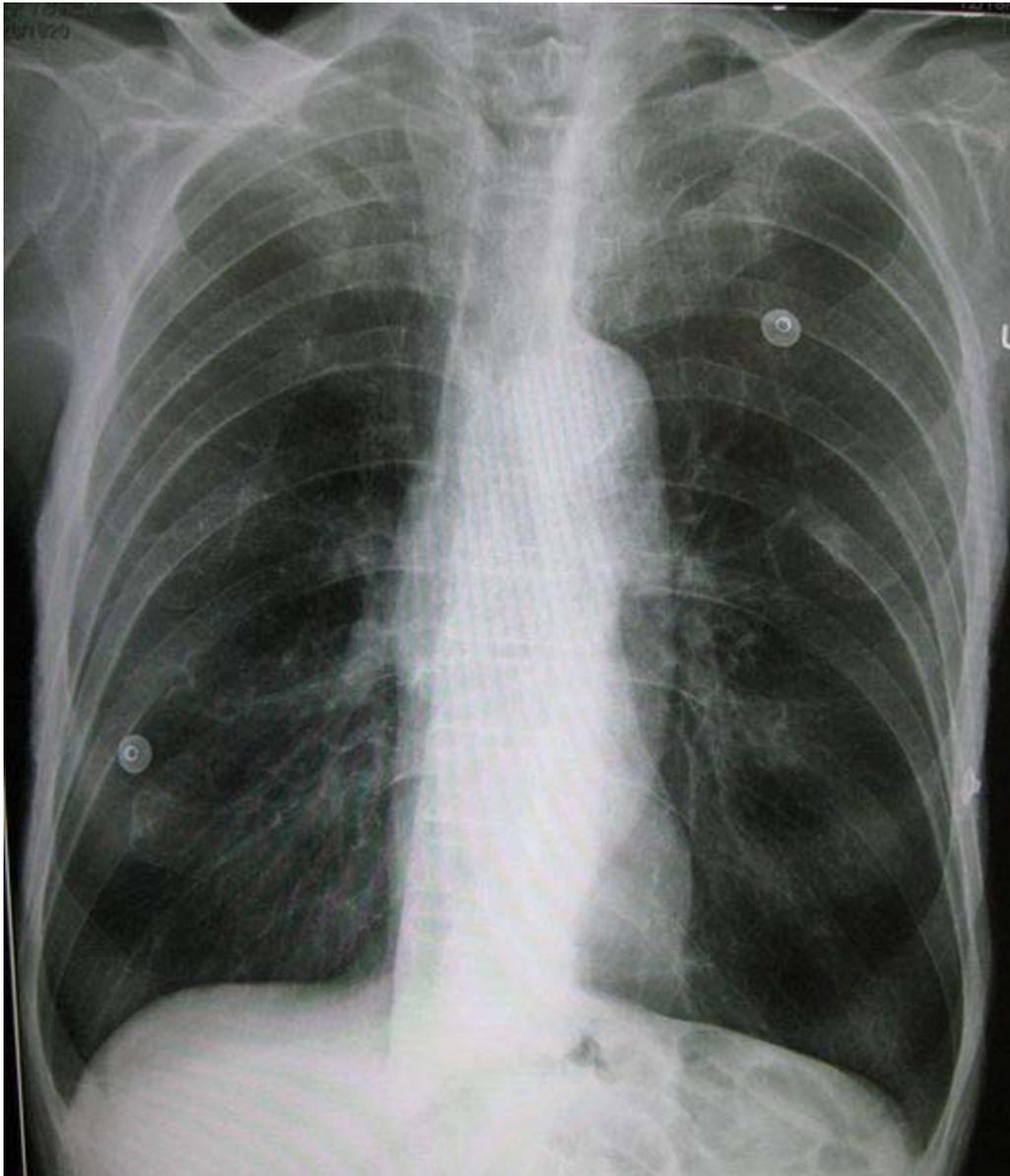
The diagnosis is usually confirmed by pulmonary function testing (e.g. spirometry); however, X-ray radiography may aid in the diagnosis. A DLCO test may be used to differentiate Emphysema from other types of Obstructive disorders such as Chronic Bronchitis and Asthma. DLCO is a test that measures the ability of gases to diffuse across the alveolar-capillary membrane. A DLCO will be decreased in Emphysema whereas it will be normal or increased in Asthma and Chronic Bronchitis.



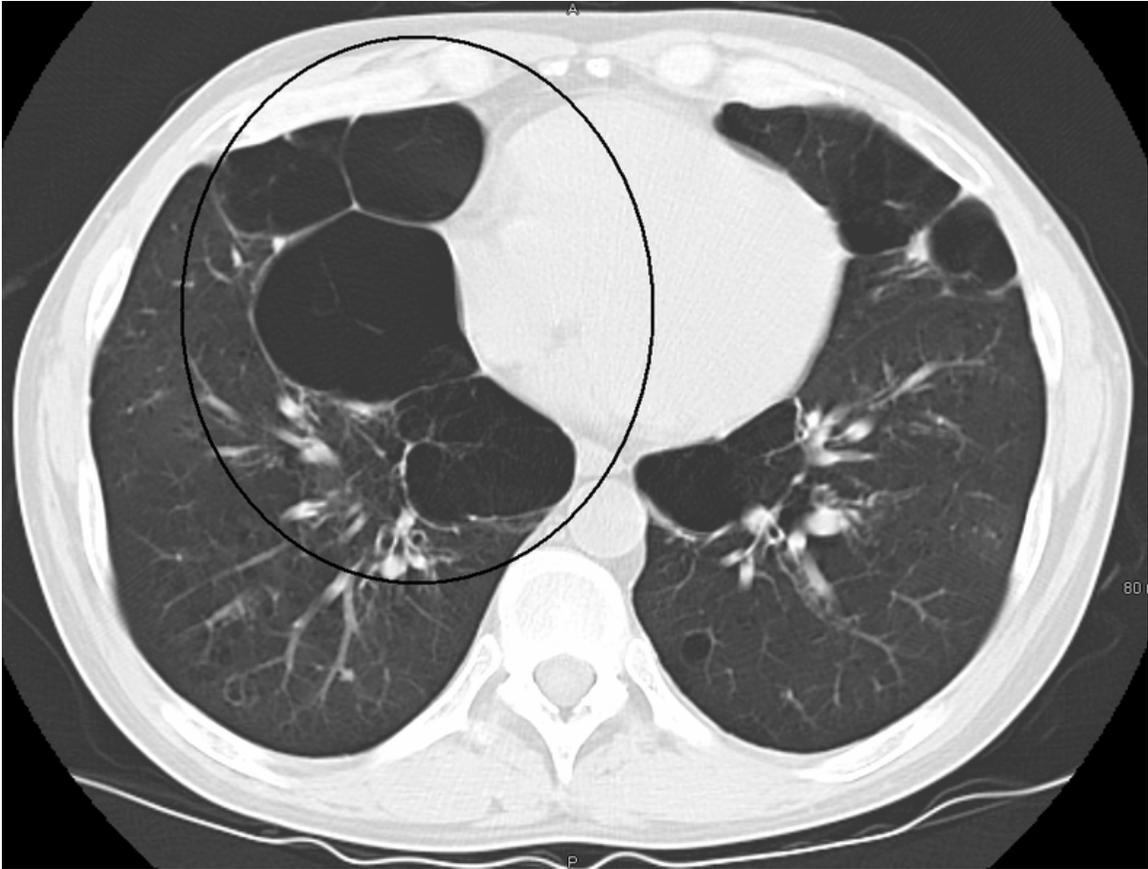
H&E stained lung tissue of end-stage emphysema. RBCs are red, nuclei are purple, other material is pink, and air spaces are white.



Micrograph demonstrating emphysema (left of image - large empty spaces) and lung tissue with relative preservation of the alveoli (right of image). H&E stain.



A severe case of emphysema



Axial CT image of the lung of a person with end-stage bullus emphysema

## ***Management***

Emphysema is also treated by supporting the breathing with anticholinergics, bronchodilators, steroid medication (inhaled or oral), effective body positioning (High Fowlers), and supplemental oxygen as required. Treating the patient's other conditions including gastric reflux and allergies may improve lung function. Supplemental oxygen used as prescribed (usually more than 20 hours per day) is the only non-surgical treatment which has been shown to prolong life in emphysema patients. There are lightweight portable oxygen systems which allow patients increased mobility. Patients can fly, cruise, and work while using supplemental oxygen. Other medications are being researched.

Lung volume reduction surgery (LVRS) can improve the quality of life for certain carefully selected patients. It can be done by different methods, some of which are minimally invasive. In July 2006 a new treatment, placing tiny valves in passages leading to diseased lung areas, was announced to have good results, but 7% of patients suffered partial lung collapse. The only known "cure" for emphysema is lung transplant, but few patients are strong enough physically to survive the surgery. The combination of a patient's age, oxygen deprivation and the side-effects of the medications used to treat emphysema cause damage to the kidneys, heart and other organs. Surgical transplantation

also requires the patient to take an anti-rejection drug regimen which suppresses the immune system, and can lead to microbial infection of the patient. Patients who think they may have contracted the disease are recommended to seek medical attention as soon as possible.

Emphysema is an irreversible degenerative condition. The most important measure to slow its progression is for the patient to stop smoking and avoid all exposure to cigarette smoke and lung irritants. Pulmonary rehabilitation can be very helpful to optimize the patient's quality of life and teach the patient how to actively manage his or her care.

## Chapter 17

# Chronic Obstructive Pulmonary Disease

### Chronic Obstructive Pulmonary Disease



Gross pathology of a lung showing centrilobular-type emphysema characteristic of smoking. This close-up of the fixed, cut lung surface shows multiple cavities lined by heavy black carbon deposits.

ICD-10	J40. - J44., J47.
ICD-9	490 - 492, 494 - 496
OMIM	606963
DiseasesDB	2672
MedlinePlus	000091
eMedicine	med/373 emerg/99
MeSH	C08.381.495.389

**Chronic obstructive pulmonary disease (COPD)**, also known as **chronic obstructive lung disease (COLD)**, **chronic obstructive airway disease (COAD)**, **chronic airflow limitation (CAL)** and **chronic obstructive respiratory disease (CORD)**, refers to

chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs causing shortness of breath. In clinical practice, COPD is defined by its characteristically low airflow on lung function tests. In contrast to asthma, this limitation is poorly reversible and usually gets progressively worse over time. In England, an estimated 842,100 of 50 million people have a diagnosis of COPD; translating into approximately one person in 59 receiving a diagnosis of COPD at some point in their lives.

COPD is caused by noxious particles or gas, most commonly from tobacco smoking, which triggers an abnormal inflammatory response in the lung. The inflammatory response in the larger airways is known as chronic bronchitis, which is diagnosed clinically when people regularly cough up sputum. In the alveoli, the inflammatory response causes destruction of the tissues of the lung, a process known as emphysema. The natural course of COPD is characterized by occasional sudden worsenings of symptoms called acute exacerbations, most of which are caused by infections or air pollution.

The diagnosis of COPD requires lung function tests. Important management strategies are smoking cessation, vaccinations, rehabilitation, and drug therapy (often using inhalers). Some patients go on to require long-term oxygen therapy or lung transplantation.

Worldwide, COPD ranked as the sixth leading cause of death in 1990. It is projected to be the fourth leading cause of death worldwide by 2030 due to an increase in smoking rates and demographic changes in many countries. COPD is the fourth leading cause of death in the U.S. and the economic burden of COPD in the U.S. in 2007 was \$42.6 billion in health care costs and lost productivity.

## ***Classification***

The twofold nature of the pathology has been studied in the past. Furthermore, also in recent studies, many authors found that each patient could be classified as presenting a predominantly bronchial or emphysematous phenotype simply analyzing clinical, functional, and radiological findings or studying interesting biomarkers. A statistical model reflecting the specific predominant mechanism of airflow limitation for a specific patient has been developed and trained over a database of hundreds of patients. The model is available here as a free online application.

## **Chronic bronchitis**

Lung damage and inflammation in the large airways results in chronic bronchitis. Chronic bronchitis is defined in clinical terms as a cough with sputum production on most days for 3 months of a year, for 2 consecutive years. In the airways of the lung, the hallmark of chronic bronchitis is an increased number (hyperplasia) and increased size (hypertrophy) of the goblet cells and mucous glands of the airway. As a result, there is more mucus than usual in the airways, contributing to narrowing of the airways and

causing a cough with sputum. Microscopically there is infiltration of the airway walls with inflammatory cells. Inflammation is followed by scarring and remodeling that thickens the walls and also results in narrowing of the airways. As chronic bronchitis progresses, there is squamous metaplasia (an abnormal change in the tissue lining the inside of the airway) and fibrosis (further thickening and scarring of the airway wall). The consequence of these changes is a limitation of airflow.

Patients with advanced COPD that have primarily chronic bronchitis rather than emphysema were commonly referred to as "Blue Bloaters" because of the bluish color of the skin and lips (cyanosis) seen in them. The hypoxia and fluid retention leads to them being called "Blue Bloaters".

## **Emphysema**

Lung damage and inflammation of the air sacs (alveoli) results in emphysema. Emphysema is defined as enlargement of the air spaces distal to the terminal bronchioles, with destruction of their walls. The destruction of air space walls reduces the surface area available for the exchange of oxygen and carbon dioxide during breathing. It also reduces the elasticity of the lung itself, which results in a loss of support for the airways that are embedded in the lung. These airways are more likely to collapse causing further limitation to airflow. The effort made by patients suffering from emphysema during exhalation, causes a pink color in their faces, hence the term commonly used to refer to them, "Pink Puffers".

## ***Signs and symptoms***

Essentials of diagnosis include:

- History of cigarette smoking.
- Chronic cough and sputum production (in chronic bronchitis)
- Dyspnea (in emphysema)
- Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination
- Airflow limitation on pulmonary function testing that is not fully reversible and most often progressive

One of the most common symptoms of COPD is shortness of breath (dyspnea). People with COPD commonly describe this as: "My breathing requires effort," "I feel out of breath," or "I can't get enough air in". People with COPD typically first notice dyspnea during vigorous exercise when the demands on the lungs are greatest. Over the years, dyspnea tends to get gradually worse so that it can occur during milder, everyday activities such as housework. In the advanced stages of COPD, dyspnea can become so bad that it occurs during rest and is constantly present.

Other symptoms of COPD are a persistent cough, sputum or mucus production, wheezing, chest tightness, and tiredness.

People with advanced (very severe) COPD sometimes develop respiratory failure. When this happens, cyanosis, a bluish discoloration of the lips caused by a lack of oxygen in the blood, can occur. An excess of carbon dioxide in the blood can cause headaches, drowsiness or twitching (asterixis). A complication of advanced COPD is cor pulmonale, a strain on the heart due to the extra work required by the heart to pump blood through the affected lungs. Symptoms of cor pulmonale are peripheral edema, seen as swelling of the ankles, and dyspnea.

There are a few signs of COPD that a healthcare worker may detect although they can be seen in other diseases. Some people have COPD and have none of these signs. Common signs are:

- tachypnea, a rapid breathing rate
- wheezing sounds or crackles in the lungs heard through a stethoscope
- breathing out taking a longer time than breathing in
- enlargement of the chest, particularly the front-to-back distance (hyperaeration)
- active use of muscles in the neck to help with breathing
- breathing through pursed lips
- increased anteroposterior to lateral ratio of the chest (i.e. barrel chest).

## **Cause**

### **Smoking**

The primary risk factor for COPD is chronic tobacco smoking. In the United States, 80 to 90% of cases of COPD are due to smoking. Exposure to cigarette smoke is measured in pack-years, the average number of packages of cigarettes smoked daily multiplied by the number of years of smoking. The likelihood of developing COPD increases with age and cumulative smoke exposure, and almost all life-long smokers will develop COPD, provided that smoking-related, extrapulmonary diseases (cardiovascular, diabetes, cancer) do not claim their lives beforehand.

### **Occupational exposures**

Intense and prolonged exposure to workplace dusts found in coal mining, gold mining, and the cotton textile industry and chemicals such as cadmium, isocyanates, and fumes from welding have been implicated in the development of airflow obstruction, even in nonsmokers. Workers who smoke and are exposed to these particles and gases are even more likely to develop COPD. Intense silica dust exposure causes silicosis, a restrictive lung disease distinct from COPD; however, less intense silica dust exposures have been linked to a COPD-like condition. The effect of occupational pollutants on the lungs appears to be substantially less important than the effect of cigarette smoking.

## **Air pollution**

Studies in many countries have found people who live in large cities have a higher rate of COPD compared to people who live in rural areas. Urban air pollution may be a contributing factor for COPD, as it is thought to slow the normal growth of the lungs, although the long-term research needed to confirm the link has not been done. Studies of the industrial waste gas and COPD/asthma-aggravating compound, sulfur dioxide, and the inverse relation to the presence of the blue lichen *Xanthoria* (usually found abundantly in the countryside, but never in towns or cities) have been seen to suggest combustive industrial processes do not aid COPD sufferers. In many developing countries, indoor air pollution from cooking fire smoke (often using biomass fuels such as wood and animal dung) is a common cause of COPD, especially in women.

## **Genetics**

Some factor in addition to heavy smoke exposure is required for a person to develop COPD. This factor is probably a genetic susceptibility. COPD is more common among relatives of COPD patients who smoke than unrelated smokers. The genetic differences that make some peoples' lungs susceptible to the effects of tobacco smoke are mostly unknown. Alpha 1-antitrypsin deficiency is a genetic condition that is responsible for about 2% of cases of COPD. In this condition, the body does not make enough of a protein, alpha 1-antitrypsin. Alpha 1-antitrypsin protects the lungs from damage caused by protease enzymes, such as elastase and trypsin, that can be released as a result of an inflammatory response to tobacco smoke.

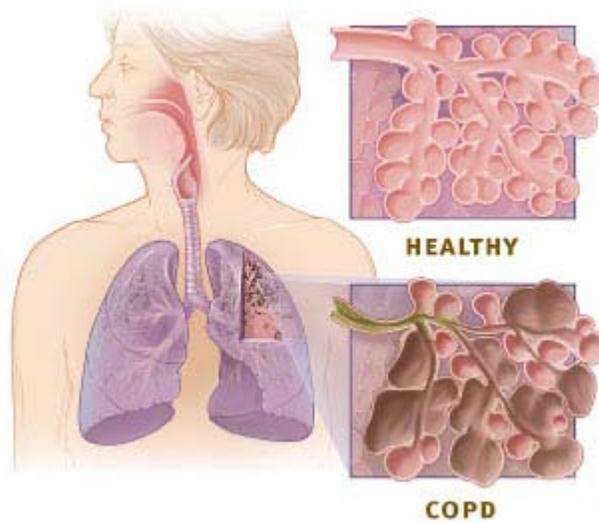
## **Other risk factors**

A tendency to sudden airway constriction in response to inhaled irritants, bronchial hyperresponsiveness, is a characteristic of asthma. Many people with COPD also have this tendency. In COPD, the presence of bronchial hyperresponsiveness predicts a worse course of the disease. It is not known if bronchial hyperresponsiveness is a cause or a consequence of COPD. Other risk factors such as repeated lung infection and possibly a diet high in cured meats (possibly due to the preservative sodium nitrite) may be related to the development of COPD.

## **Autoimmune disease**

There is mounting evidence that there may be an autoimmune component to COPD, triggered by lifelong smoking. Many individuals with COPD who have stopped smoking have active inflammation in the lungs. The disease may continue to get worse for many years after stopping smoking due to this ongoing inflammation. This sustained inflammation is thought to be mediated by autoantibodies and autoreactive T cells.

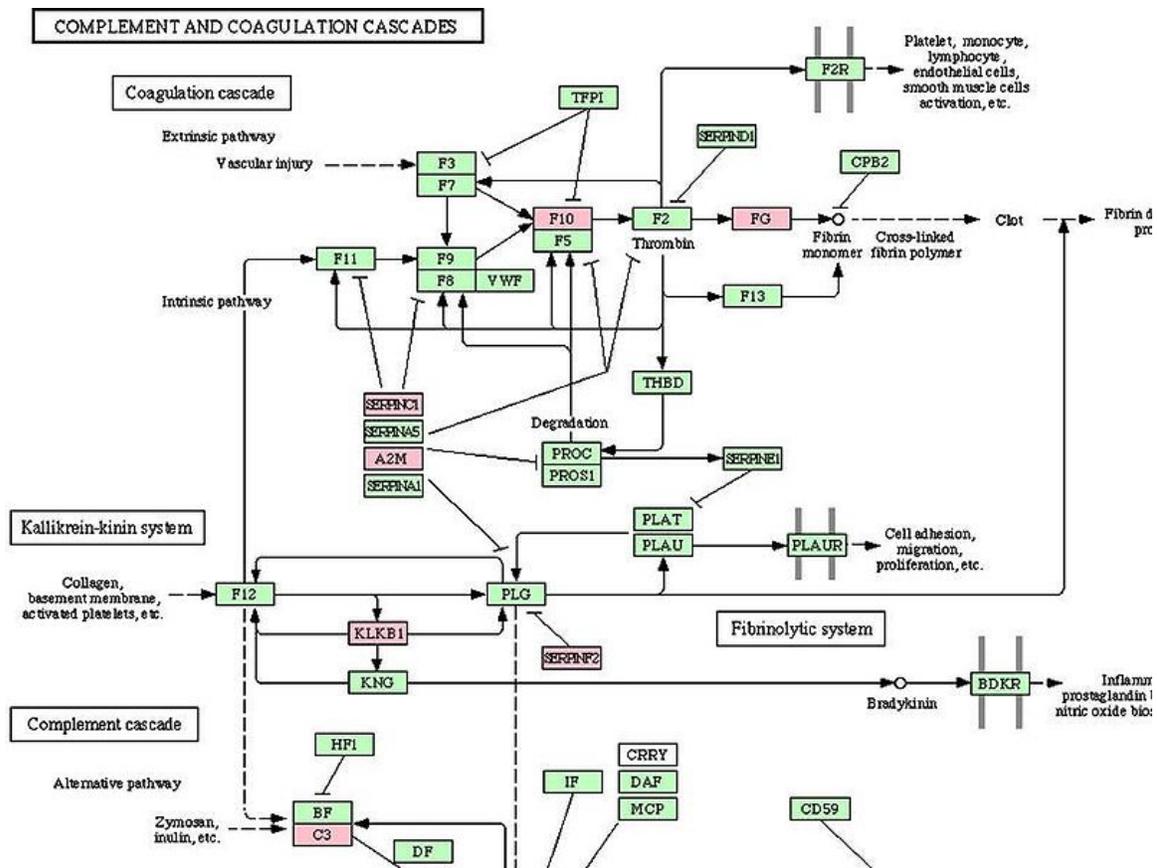
## ***Pathophysiology***



Enlarged view of lung tissue showing the difference between healthy lung and COPD

It is not fully understood how tobacco smoke and other inhaled particles damage the lungs to cause COPD. The most important processes causing lung damage are:

- Oxidative stress produced by the high concentrations of free radicals in tobacco smoke
- Cytokine release due to inflammation as the body responds to irritant particles such as tobacco smoke in the airway
- Tobacco smoke and free radicals impair the activity of antiprotease enzymes such as alpha 1-antitrypsin, allowing protease enzymes to damage the lung



Potential role of coagulation and the complement system in COPD; a complex cascade of blood plasma proteins and platelet activation as molecular perturbations associated with patients suffering from COPD

Narrowing of the airways reduces the rate at which air can flow to and from the air sacs (alveoli) and limits the effectiveness of the lungs. In COPD, the greatest reduction in air flow occurs when breathing out (during expiration) because the pressure in the chest tends to compress rather than expand the airways. In theory, air flow could be increased by breathing more forcefully, increasing the pressure in the chest during expiration. In COPD, there is often a limit to how much this can actually increase air flow, a situation known as expiratory flow limitation.

If the rate of airflow is too low, a person with COPD may not be able to completely finish breathing out (expiration) before he or she needs to take another breath. This is particularly common during exercise, when breathing has to be faster. A little of the air of the previous breath remains within the lungs when the next breath is started, resulting in an increase in the volume of air in the lungs, a process called dynamic hyperinflation.

Dynamic hyperinflation is closely linked to dyspnea in COPD. It is less comfortable to breathe with hyperinflation because it takes more effort to move the lungs and chest wall when they are already stretched by hyperinflation.

Another factor contributing to shortness of breath in COPD is the loss of the surface area available for the exchange of oxygen and carbon dioxide with emphysema. This reduces the rate of transfer of these gases between the body and the atmosphere and can lead to low oxygen and high carbon dioxide levels in the body. A person with emphysema may have to breathe faster or more deeply to compensate, which can be difficult to do if there is also flow limitation or hyperinflation.

Some people with advanced COPD do manage to breathe fast to compensate, but usually have dyspnea as a result. Others, who may be less short of breath, tolerate low oxygen and high carbon dioxide levels in their bodies, but this can eventually lead to headaches, drowsiness and heart failure.

Advanced COPD can lead to complications beyond the lungs, such as weight loss (cachexia), pulmonary hypertension and right-sided heart failure (cor pulmonale). Osteoporosis, heart disease, muscle wasting and depression are all more common in people with COPD.

Several molecular signatures associated to lung function decline and corollaries of disease severity have been proposed, a majority of which are characterized in easily accessible surrogate tissue, including blood derivatives such as serum and plasma. A recent 2010 clinical study proposes alpha 1B-glycoprotein precursor/A1BG, alpha 2-antiplasmin, apolipoprotein A-IV precursor/APOA4, and complement component 3 precursor, among other coagulation and complement system proteins as corollaries of lung function decline, although ambiguity between cause and effect is unresolved.

### **Acute exacerbations of COPD**

An acute exacerbation of COPD is a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) that typically lasts for several days. It may be triggered by an infection with bacteria or viruses or by environmental pollutants. Typically, infections cause 75% or more of the exacerbations; bacteria can roughly be found in 25% of cases, viruses in another 25%, and both viruses and bacteria in another 25%. Pulmonary emboli can also cause exacerbations of COPD. Airway inflammation is increased during the exacerbation, resulting in increased hyperinflation, reduced expiratory air flow and worsening of gas transfer. This can also lead to hypoventilation and eventually hypoxia, insufficient tissue perfusion, and then cell necrosis.

## ***Diagnosis***



A chest X-ray demonstrating severe COPD. Note the small size of the heart in comparison to the lungs.

The diagnosis of COPD should be considered in anyone who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease such as regular tobacco smoking. No single symptom or sign can adequately confirm or exclude the diagnosis of COPD, although COPD is uncommon under the age of 40 years.

## Spirometry

The diagnosis of COPD is confirmed by spirometry, a test that measures the forced expiratory volume in one second (FEV<sub>1</sub>), which is the greatest volume of air that can be breathed out in the first second of a large breath. Spirometry also measures the forced vital capacity (FVC), which is the greatest volume of air that can be breathed out in a whole large breath. Normally, at least 70% of the FVC comes out in the first second (i.e. the FEV<sub>1</sub>/FVC ratio is >70%). A ratio less than normal defines the patient as having COPD. More specifically, the diagnosis of COPD is made when the FEV<sub>1</sub>/FVC ratio is <70%. The GOLD criteria also require that values are after bronchodilator medication has been given to make the diagnosis, and the NICE criteria also require FEV<sub>1</sub>%. According to the ERS criteria, it is FEV<sub>1</sub>% predicted that defines when a patient has COPD, that is, when FEV<sub>1</sub>% predicted is < 88% for men, or < 89% for women.

Spirometry can help to determine the severity of COPD. The FEV<sub>1</sub> (measured after bronchodilator medication) is expressed as a percentage of a predicted "normal" value based on a person's age, gender, height and weight:

Severity of COPD	FEV <sub>1</sub> % predicted
Mild	≥80
Moderate	50–79
Severe	30–49
Very severe	<30 or chronic respiratory failure symptoms

The severity of COPD also depends on the severity of dyspnea and exercise limitation. These and other factors can be combined with spirometry results to obtain a COPD severity score that takes multiple dimensions of the disease into account.

## Other tests

On chest x-ray, the classic signs of COPD are overexpanded lung (hyperinflation), a flattened diaphragm, increased retrosternal airspace, and bullae. It can be useful to help exclude other lung diseases, such as pneumonia, pulmonary edema or a pneumothorax. Complete pulmonary function tests with measurements of lung volumes and gas transfer may also show hyperinflation and can discriminate between COPD with emphysema and COPD without emphysema. A high-resolution computed tomography scan of the chest may show the distribution of emphysema throughout the lungs and can also be useful to exclude other lung diseases.

A blood sample taken from an artery can be tested for blood gas levels which may show low oxygen levels (hypoxemia) and/or high carbon dioxide levels (respiratory acidosis). A blood sample taken from a vein may show a high blood count (reactive polycythemia), a reaction to long-term hypoxemia.

## **Management**

There is currently no cure for COPD; however, COPD is both a preventable and treatable disease. Clinical practice guidelines for the management of COPD are available from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a collaboration that includes the World Health Organization and the U.S. National Heart, Lung, and Blood Institute. The major current directions of COPD management are to assess and monitor the disease, reduce the risk factors, manage stable COPD, prevent and treat acute exacerbations and manage comorbidity.

The only measures that have been shown to reduce mortality is smoking cessation and supplemental oxygen.

## **Risk factor reduction**

### **Smoking cessation**

Smoking cessation is one of the most important factors in slowing down the progression of COPD. Once COPD has been diagnosed, stopping smoking slows down the rate of progression of the disease. Even at a late stage of the disease, it can significantly reduce the rate of deterioration in lung function and delay the onset of disability and death. It is the only standard intervention that can improve the rate of progression of COPD.

Smoking cessation starts with an individual decision to stop smoking that leads to an attempt at quitting. Often several attempts are required before long-term smoking cessation is achieved. Some smokers can achieve long-term smoking cessation through "willpower" alone. However, smoking is highly addictive, and many smokers need further support to quit. The chance of successfully stopping smoking can be greatly improved through social support, engagement in a smoking cessation programme and the use of drugs such as nicotine replacement therapy, bupropion and varenicline.

The policies of governments, public health agencies and antismoking organizations can reduce smoking rates by encouraging smoking cessation and discouraging people from starting smoking. These policies are important strategies in the prevention of COPD.

### **Occupational health**

Measures can be taken to reduce the likelihood that workers in at-risk industries such as coal mining will develop COPD. Some examples of these measures are: education of workers and management about the risks, promoting smoking cessation, surveillance of workers for early signs of COPD, the use of personal dust monitors, the use of respirators and dust control. Dust control can be achieved by improving ventilation, using water sprays and by using mining techniques that minimize dust generation. If a worker develops COPD, further lung damage can be reduced by avoiding ongoing dust exposure, for example by changing the work role.

## **Air pollution**

Air quality can be improved by pollution reduction efforts which should lead to health gains for people with COPD. A person who has COPD may experience fewer symptoms if they stay indoors on days when air quality is poor.

## **Bronchodilators**

Bronchodilators are medicines that relax smooth muscle around the airways, increasing the calibre of the airways and improving air flow. They can reduce the symptoms of shortness of breath, wheeze and exercise limitation, resulting in an improved quality of life for people with COPD. They do not slow down the rate of progression of the underlying disease. Bronchodilators are usually administered with an inhaler or via a nebulizer.

There are two major types of bronchodilator,  $\beta_2$  agonists and anticholinergics. Anticholinergics appear to be superior to  $\beta_2$  agonists in COPD. Anticholinergics reduce respiratory deaths while  $\beta_2$  agonists have no effect on respiratory deaths. Each type may be either long-acting (with an effect lasting 12 hours or more) or short-acting (with a rapid onset of effect that does not last as long).

## **$\beta_2$ agonists**

$\beta_2$  agonists stimulate  $\beta_2$  receptors on airway smooth muscles, causing them to relax. There are several  $\beta_2$  agonists available. Salbutamol (common brand name: Ventolin) and terbutaline are widely used short acting  $\beta_2$  agonists and provide rapid relief of COPD symptoms. Long acting  $\beta_2$  agonists (LABAs) such as salmeterol and formoterol are used as maintenance therapy and lead to improved airflow, exercise capacity, and quality of life.

## **Anticholinergics**

Anticholinergic drugs cause airway smooth muscles to relax by blocking stimulation from cholinergic nerves. Ipratropium is the most widely prescribed short acting anticholinergic drug. Like short-acting  $\beta_2$  agonists, short-acting anticholinergics provide rapid relief of COPD symptoms and a combination of the two is commonly used for a greater bronchodilator effect. Tiotropium is the most commonly prescribed long-acting anticholinergic drug in COPD. It has more specificity for  $M_3$  muscarinic receptors, so may have fewer side effects than other anticholinergic drugs. Regular use is associated with improvements in airflow, exercise capacity, quality of life and possibly a longer life. In January 2010, new research showed ipratropium used to treat COPD increased cardiovascular morbidity. At the same time tiotropium was shown to be effective in eliminating the risk of all cause mortality, cardiovascular mortality and cardiovascular events.

## **Corticosteroids**

Corticosteroids act to reduce the inflammation in the airways, in theory reducing lung damage and airway narrowing caused by inflammation. Unlike bronchodilators, they do not act directly on the airway smooth muscle and do not provide immediate relief of symptoms. Some of the more common corticosteroids in use are prednisone, fluticasone, budesonide, mometasone, and beclomethasone. Corticosteroids are used in tablet or inhaled form to treat and prevent acute exacerbations of COPD. Well-inhaled corticosteroids (ICS) have not been shown to be of benefit for people with mild COPD, however, they have been shown to decrease acute exacerbations in those with either moderate or severe COPD. They however have no effect on overall one-year mortality and are associated with increased rates of pneumonia.

## **Other medication**

Theophylline is a bronchodilator and phosphodiesterase inhibitor that in high doses can reduce symptoms for some people who have COPD. More often, side effects such as nausea and stimulation of the heart limit its use. In lower doses, it may slightly reduce the number of COPD exacerbations. The investigative phosphodiesterase-4 antagonists, roflumilast and cilomilast have completed Phase-2 clinical trials. Tumor necrosis factor antagonists such as infliximab suppress the immune system and reduce inflammation. Infliximab has been trialled in COPD but there was no evidence of benefit with the possibility of harm.

## Supplemental oxygen



Oxygen can be delivered in different forms: in large containers, in smaller containers with liquid oxygen, or with the use of an oxygen concentrator (*shown here*) which derives oxygen from room air. The latter two options improve mobility of people requiring long-term oxygen therapy.

Supplemental oxygen can be given to people with COPD who have low oxygen levels in the body. Oxygen is provided from an oxygen cylinder or an oxygen concentrator and delivered to a person through tubing via a nasal cannula or oxygen mask. Supplemental oxygen does not greatly improve shortness of breath but can allow people with COPD and low oxygen levels to do more exercise and household activity. Long-term oxygen therapy for at least 16 hours a day can improve the quality of life and survival for people with COPD and arterial hypoxemia or with complications of hypoxemia such as

pulmonary hypertension, cor pulmonale, or secondary erythrocytosis. High concentrations of supplemental oxygen can lead to the accumulation of carbon dioxide and respiratory acidosis for some people with severe COPD; lower oxygen flow rates are generally safer for these individuals.

## **Pulmonary rehabilitation**

Pulmonary rehabilitation is a program of exercise, disease management and counselling coordinated to benefit the individual. Pulmonary rehabilitation has been shown to improve shortness of breath and exercise capacity. It has also been shown to improve the sense of control a patient has over their disease as well as their emotions.

## **Nutrition**

Being either underweight or overweight can affect the symptoms, degree of disability and prognosis of COPD. People with COPD who are underweight can improve their breathing muscle strength by increasing their calorie intake. When combined with regular exercise or a pulmonary rehabilitation programme, this can lead to improvements in COPD symptoms.

## **Surgery**

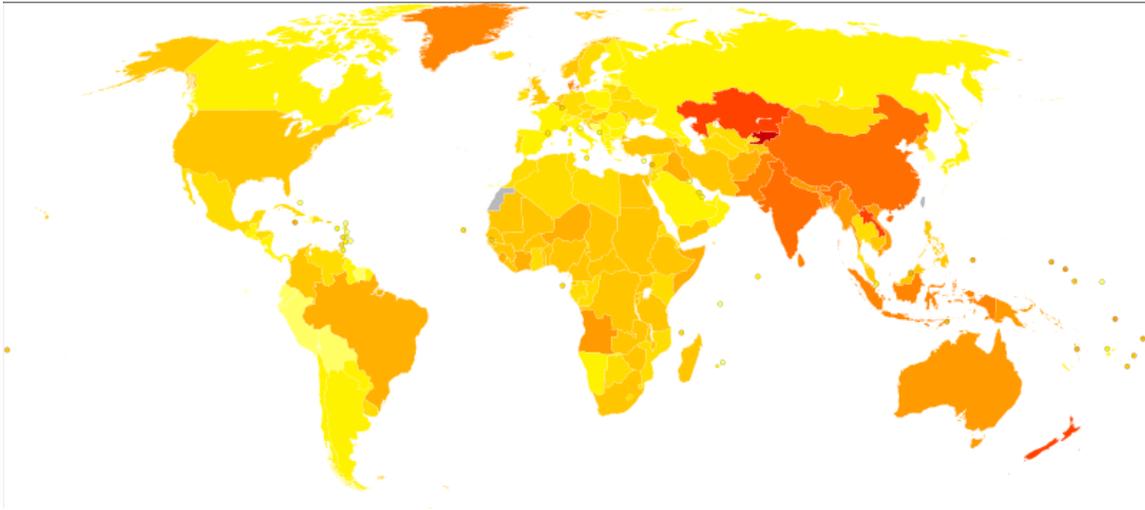
Surgery is sometimes helpful for COPD in selected cases. A bullectomy is the surgical removal of a bulla, a large air-filled space that can squash the surrounding, more normal lung. Lung volume reduction surgery is similar; parts of the lung that are particularly damaged by emphysema are removed allowing the remaining, relatively good lung to expand and work better. Lung transplantation is sometimes performed for severe COPD, particularly in younger individuals.

## ***Prognosis***

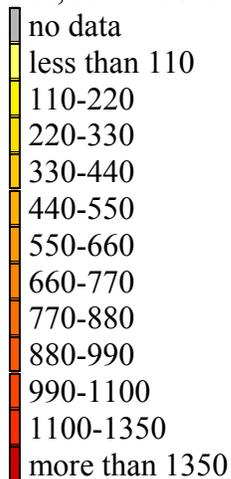
COPD usually gradually gets worse over time and can lead to death. The rate at which it gets worse varies between individuals. The factors that predict a poorer prognosis are:

- Severe airflow obstruction (low FEV<sub>1</sub>)
- Poor exercise capacity
- Shortness of breath
- Significantly underweight or overweight
- Complications like respiratory failure or cor pulmonale
- Continued smoking
- Frequent acute exacerbations

## **Epidemiology**



Disability-adjusted life year for chronic obstructive pulmonary disease per 100,000 inhabitants in 2004.



COPD occurs in 34 out of 1000 greater than 65 years old. In England, an estimated 842,100 of 50 million people have a diagnosis of COPD; translating into approximately one person in 59 receiving a diagnosis of COPD at some point in their lives. In the most socioeconomically deprived parts of the country, one in 32 people were diagnosed with COPD, compared with one in 98 in the most affluent areas. In the United States, the prevalence of COPD is approximately 1 in 20 or 5%, totalling approximately 13.5 million people in USA, or possibly approximately 25 million people if undiagnosed cases are included.

## **History**

COPD has probably always existed but has been called by different names in the past. Bonet described a condition of “voluminous lungs” in 1679. In 1769, Giovanni Morgagni described 19 cases where the lungs were “turgid” particularly from air. The first

description and illustration of the enlarged airspaces in emphysema was provided by Ruysh in 1721. "History of pathologic descriptions of COPD" (PDF). Matthew Baillie illustrated an emphysematous lung in 1789 and described the destructive character of the condition. Badham used the word "catarrh" to describe the cough and mucus hypersecretion of chronic bronchitis in 1814. He recognised that chronic bronchitis was a disabling disorder.

René Laennec, the physician who invented the stethoscope, used the term "emphysema" in his book *A Treatise on the Diseases of the Chest and of Mediate Auscultation* (1837) to describe lungs that did not collapse when he opened the chest during an autopsy. He noted that they did not collapse as usual because they were full of air and the airways were filled with mucus.

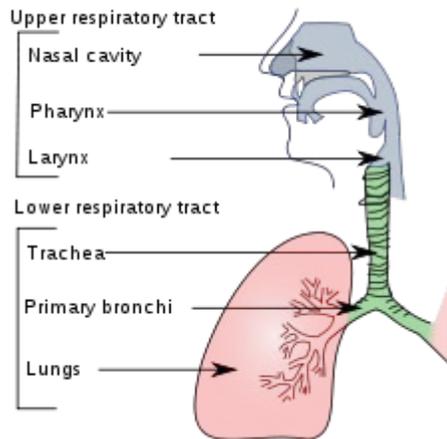
In 1842, John Hutchinson invented the spirometer, which allowed the measurement of vital capacity of the lungs. However, his spirometer could only measure volume, not airflow. Tiffeneau in 1947 and Gaensler in 1950 and 1951 described the principles of measuring airflow.

The terms chronic bronchitis and emphysema were formally defined at the CIBA guest symposium of physicians in 1959. The term COPD was first used by William Briscoe in 1965 and has gradually overtaken other terms to become established today as the preferred name for this disease.

## Chapter 18

# Upper Respiratory Tract Infection

### Upper respiratory tract infection



Conducting passages.

**ICD-10** J00-06., J30-39.

**ICD-9** 465.9

**Upper respiratory tract infections (URI or URTI)** are the illnesses caused by an acute infection which involves the upper respiratory tract: nose, sinuses, pharynx or larynx. This commonly includes: tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, and the common cold.

### **Definitions**

Common URI terms are defined as follows:

- Rhinitis - Inflammation of the nasal mucosa
- Rhinosinusitis or sinusitis - Inflammation of the nares and paranasal sinuses, including frontal, ethmoid, maxillary, and sphenoid

- Nasopharyngitis (rhinopharyngitis or the common cold) - Inflammation of the nares, pharynx, hypopharynx, uvula, and tonsils
- Pharyngitis - Inflammation of the pharynx, hypopharynx, uvula, and tonsils
- Epiglottitis (supraglottitis) - Inflammation of the superior portion of the larynx and supraglottic area
- Laryngitis - Inflammation of the larynx
- Laryngotracheitis - Inflammation of the larynx, trachea, and subglottic area
- Tracheitis - Inflammation of the trachea and subglottic area

## **Signs and symptoms**

Acute upper respiratory tract infections include rhinitis, pharyngitis/tonsillitis and laryngitis often referred to as a common cold, and their complications: sinusitis, ear infection and sometimes bronchitis (though bronchi are generally classified as part of the lower respiratory tract.) Symptoms of URI's commonly include cough, sore throat, runny nose, nasal congestion, headache, low grade fever, facial pressure and sneezing. Onset of the symptoms usually begins 1–3 days after the exposure to a microbial pathogen. The illness usually lasts 7–10 days.

Group A beta hemolytic streptococcal pharyngitis/tonsillitis(strep throat) typically presents with a sudden onset of sore throat, pain with swallowing and fever. Strep throat does not usually cause runny nose, voice changes or cough.

Pain and pressure of the ear caused by a middle ear infection (Otitis media) and the reddening of the eye caused by viral Conjunctivitis are often associated with upper respiratory infections.

URI, seasonal allergies, influenza: symptom comparison

<b>Symptoms</b>	<b>Allergy</b>	<b>URI</b>	<b>Influenza</b>
Itchy, watery eyes	Common	Rare (conjunctivitis may occur with adenovirus)	Soreness behind eyes, sometimes conjunctivitis
Nasal discharge	Common	Common	Common
Nasal congestion	Common	Common	Sometimes
Sneezing	Very common	Very common	Sometimes
Sore throat	Sometimes (postnasal drip)	Very common	Sometimes
Cough	Sometimes	Common (mild to moderate, hacking)	Common (dry cough, can be severe)
Headache	Uncommon	Rare	Common
Fever	Never	Rare in adults, possible in children	Very common (100-102°F (or higher in young children), lasting

Malaise	Sometimes	Sometimes	3–4 days; may have chills) Very common
Fatigue, weakness	Sometimes	Sometimes	Very common, can last for weeks, extreme exhaustion early in course
Muscle pain	Never	Slight	Very common, often severe

## **Cause**

Over 200 different viruses have been isolated in patients with URIs. The most common virus is called the rhinovirus. Other viruses include the coronavirus, parainfluenza virus, adenovirus, enterovirus, and respiratory syncytial virus.

Up to 15% of acute pharyngitis cases may be caused by bacteria, commonly Group A streptococcus in Streptococcal pharyngitis ("Strep Throat").

Influenza (the flu) is a more severe systemic illness which typically involves the upper respiratory tract. Influenza is a relatively uncommon cause of influenza-like illness.

## **Treatment**

Treatment depends on the underlying cause. There are currently no medications or herbal remedies which have been conclusively demonstrated to shorten the duration of illness. Treatment comprises symptomatic support usually via analgesics for headache, sore throat and muscle aches.

There is no evidence to support the age-old advice to rest when you are sick with an upper respiratory illness. Moderate exercise in sedentary subjects with a URI has been shown to have no effect on the overall severity and duration of the illness. Based on these findings, it was concluded that previously sedentary people who have acquired a URI and who have initiated an exercise program may continue to exercise. Increasing fluid intake, or "drinking plenty of fluids" during a cold is not supported by medical evidence, according to a literature review published in the British Medical Journal.

## **Antibiotics**

Judicious use of antibiotics can decrease unnecessary adverse effects of antibiotics as well as out-of-pocket costs to the patient. But more importantly, decreased antibiotic usage will prevent the rise of drug resistant bacteria, which is now a growing problem in the world. Health authorities have been strongly encouraging physicians to decrease the prescribing of antibiotics to treat common upper respiratory tract infections because antibiotic usage does not significantly reduce recovery time for these viral illnesses. Some have advocated a delayed antibiotic approach to treating URIs which seeks to reduce the consumption of antibiotics while attempting to maintain patient satisfaction. Most studies show no difference in improvement of symptoms between those treated with antibiotics right away and those with delayed prescriptions. Most studies also show no

difference in patient satisfaction, patient complications, symptoms between delayed and no antibiotics. A strategy of "no antibiotics" results in even less antibiotic use than a strategy of "delayed antibiotics". However, in certain higher risk patients with underlying lung disease, such as chronic obstructive pulmonary disease (COPD), evidence does exist to support the treatment of bronchitis with antibiotics to shorten the course of the illness and decrease treatment failure.

## Decongestants

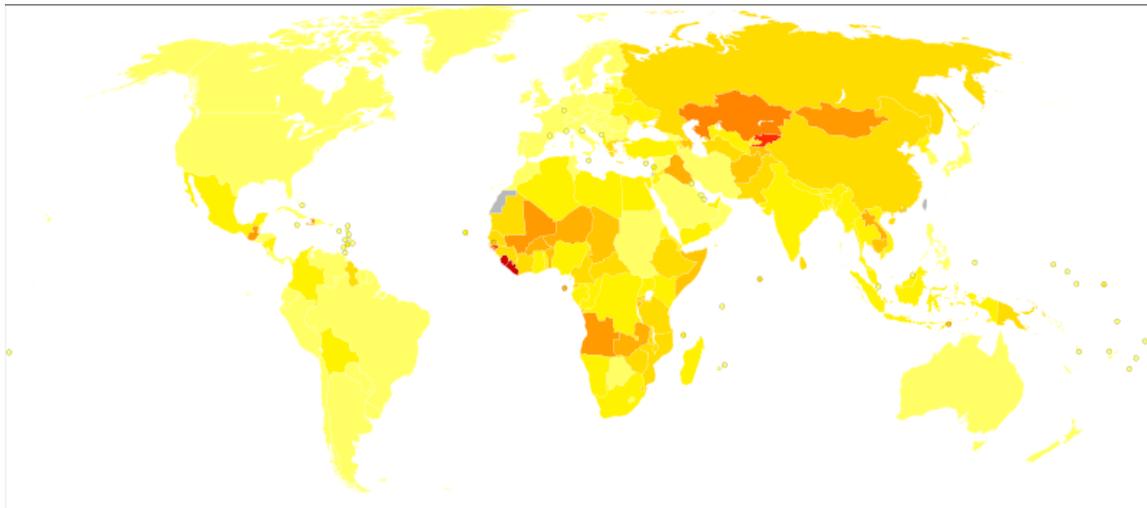
According to a Cochrane review single oral dose of nasal decongestant in the common cold is modestly effective for the short term relief of congestion in adults; however, "there is insufficient data on the use of decongestants in children." Therefore decongestants are not recommended for use in children under 12 years of age with the common cold. Oral decongestants are, also, contraindicated in patients with hypertension, coronary artery disease, and history of bleeding strokes.

## Alternative medicine

The use of Vitamin C in the inhibition and treatment of upper respiratory infections has been suggested since the initial isolation of vitamin C in the 1930s. Some evidence exists to indicate that it could be justified in persons exposed to brief periods of severe physical exercise and/or cold environments.

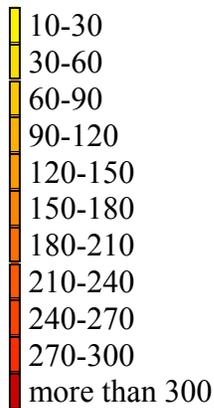
The benefits versus risk of nasal irrigation are currently unclear and therefore is not recommended.

## Epidemiology



Disability-adjusted life year for upper respiratory infections per 100,000 inhabitants in 2002.

- no data
- less than 10



Transmission is via respiratory droplets or by virus-contaminated hands. Upper respiratory tract (nose, throat, sinuses) mucosa inflammation causes increased secretions, rhinorrhea and results in sneezing, and coughing facilitating the spread.

In United States URIs are the most common infectious illness in the general population. URIs are the leading reasons for people missing work and school. URI is the leading diagnosis in the office setting.

## Chapter 19

# Acute Respiratory Distress Syndrome

### Adult respiratory distress syndrome



Chest x-ray of patient with ARDS

<b>ICD-10</b>	J80.
<b>ICD-9</b>	518.5, 518.82
<b>DiseasesDB</b>	892
<b>MedlinePlus</b>	000103
<b>eMedicine</b>	med/70
<b>MeSH</b>	D012128

**Acute respiratory distress syndrome (ARDS)**, also known as **respiratory distress syndrome (RDS)** or **adult respiratory distress syndrome** (in contrast with IRDS) is a serious reaction to various forms of injuries to the lung.

ARDS is a severe lung disease caused by a variety of direct and indirect issues. It is characterized by inflammation of the lung parenchyma leading to impaired gas exchange with concomitant systemic release of inflammatory mediators causing inflammation, hypoxemia and frequently resulting in multiple organ failure. This condition is often

fatal, usually requiring mechanical ventilation and admission to an intensive care unit. A less severe form is called acute lung injury (ALI).

ARDS formerly most commonly signified *adult respiratory distress syndrome* to differentiate it from infant respiratory distress syndrome in premature infants. However, as this type of pulmonary edema also occurs in children, *ARDS* has gradually shifted to mean *acute* rather than *adult*. The differences with the typical infant syndrome remain.

## **Definition**

### **Historical background**

Acute respiratory distress syndrome was first described in 1967 by Ashbaugh *et al.* Initially there was no definition, resulting in controversy over incidence and mortality. In 1988 an expanded definition was proposed which quantified physiologic respiratory impairment.

In 1994 a new definition was recommended by the American-European Consensus Conference Committee. It had two advantages: 1 it recognizes that severity of pulmonary injury varies, 2 it is simple to use.

ARDS was defined as the ratio of arterial partial oxygen tension ( $\text{PaO}_2$ ) as fraction of inspired oxygen ( $\text{FiO}_2$ ) below 200 mmHg in the presence of bilateral infiltrates on the chest x-ray. These infiltrates may appear similar to those of left ventricular failure, but the cardiac silhouette appears normal in ARDS. Also, the pulmonary capillary wedge pressure is normal (less than 18 mmHg) in ARDS, but raised in left ventricular failure.

A  $\text{PaO}_2/\text{FiO}_2$  ratio less than 300 mmHg with bilateral infiltrates indicates acute lung injury (ALI). Although formally considered different from ARDS, ALI is usually just a precursor to ARDS.

### **Consensus after 1967 and 1994**

ARDS is characterized by:

- Acute onset
- Bilateral infiltrates on chest radiograph sparing costophrenic angles
- Pulmonary artery wedge pressure < 18 mmHg (obtained by pulmonary artery catheterization), if this information is available; if unavailable, then lack of clinical evidence of left ventricular failure suffices
- if  $\text{PaO}_2:\text{FiO}_2 < 300$  mmHg (40 kPa) acute lung injury (ALI) is considered to be present
- if  $\text{PaO}_2:\text{FiO}_2 < 200$  mmHg (26.7 kPa) acute respiratory distress syndrome (ARDS) is considered to be present

To summarize and simplify, ARDS is an acute (rapid onset) syndrome (collection of symptoms) that affects the lungs widely and results in a severe oxygenation defect, but is not heart failure

### ***Signs and symptoms***

ARDS patients usually presents with shortness of breath, tachypnea and occasionally confusion resulting from low oxygen levels.

ARDS can occur within 24 to 48 hours of an injury (trauma, burns, aspiration, massive blood transfusion, drug/alcohol abuse) or an acute illness (infectious pneumonia, sepsis, acute pancreatitis).

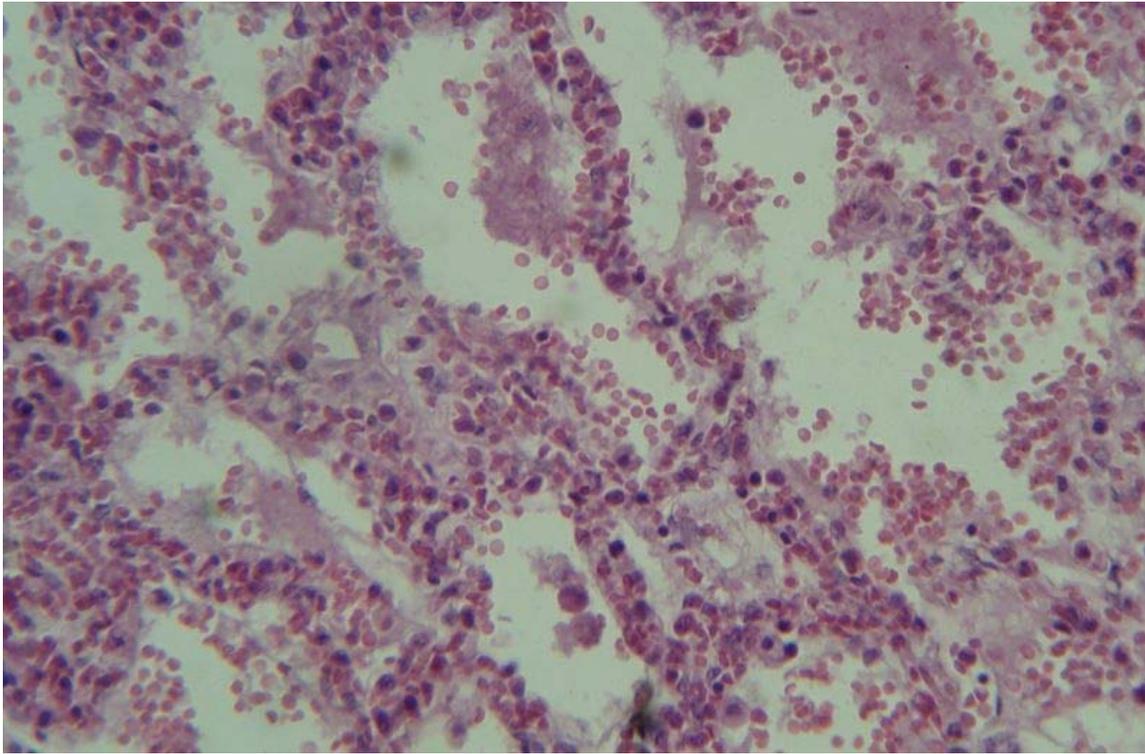
### ***Diagnosis***

An arterial blood gas analysis and chest X-ray allow formal diagnosis by the aforementioned criteria. Although severe hypoxemia is generally included, the appropriate threshold defining abnormal PaO<sub>2</sub> has never been systematically studied. Note though, that a severe oxygenation defect is not synonymous with ventilatory support. Any PaO<sub>2</sub> below 100 (generally saturation less than 100%) on a supplemental oxygen fraction of 50% meets criteria for ARDS. This can easily be achieved by high flow oxygen supplementation without ventilatory support.

Any cardiogenic cause of pulmonary edema should be excluded. This can be done by placing a pulmonary artery catheter for measuring the pulmonary artery wedge pressure. However, this is not necessary and is now rarely done as abundant evidence has emerged demonstrating that the use of pulmonary artery catheters does not lead to improved patient outcomes in critical illness including ARDS.

Plain chest X-rays are sufficient to document bilateral alveolar infiltrates in the majority of cases. While CT scanning leads to more accurate images of the pulmonary parenchyma in ARDS, it has little utility in the clinical management of patients with ARDS, and remains largely a research tool.

## ***Pathophysiology***



A pathohistological image of ARDS

ARDS is a clinical syndrome associated with a variety of pathological findings. These include pneumonia, eosinophilic pneumonia, cryptogenic organizing pneumonia, acute fibrinous organizing pneumonia, and diffuse alveolar damage (DAD). Of these, the pathology most commonly associated with ARDS is DAD.

DAD is characterized by a diffuse inflammation of lung parenchyma. The triggering insult to the parenchyma usually results in an initial release of cytokines and other inflammatory mediators, secreted by local epithelial and endothelial cells.

Neutrophils and some T-lymphocytes quickly migrate into the inflamed lung parenchyma and contribute in the amplification of the phenomenon.

Typical histological presentation involves diffuse alveolar damage and hyaline membrane formation in alveolar walls.

Although the triggering mechanisms are not completely understood, recent research has examined the role of inflammation and mechanical stress.

## Inflammation

Inflammation alone, as in sepsis, causes endothelial dysfunction, fluid extravasation from the capillaries and impaired drainage of fluid from the lungs. Dysfunction of type II pulmonary epithelial cells may also be present, with a concomitant reduction in surfactant production. Elevated inspired oxygen concentration often becomes necessary at this stage, and may facilitate a 'respiratory burst' in immune cells.

In a secondary phase, endothelial dysfunction causes cells and inflammatory exudate to enter the alveoli. This pulmonary edema increases the thickness of the alveolo-capillary space, increasing the distance the oxygen must diffuse to reach blood. This impairs gas exchange leading to hypoxia, increases the work of breathing, eventually induces fibrosis of the airspace.

Moreover, edema and decreased surfactant production by type II pneumocytes may cause whole alveoli to collapse, or to completely flood. This *loss of aeration* contributes further to the right-to-left shunt in ARDS. As the alveoli contain progressively less gas, more blood flows through them without being oxygenated resulting in massive intrapulmonary shunting.

Collapsed alveoli (and small bronchi) do not allow gas exchange. It is not uncommon to see patients with a PaO<sub>2</sub> of 60 mmHg (8.0 kPa) despite mechanical ventilation with 100% inspired oxygen.

The loss of aeration may follow different patterns according to the nature of the underlying disease, and other factors. In pneumonia-induced ARDS, for example, large, more commonly causes relatively compact areas of alveolar infiltrates. These are usually distributed to the lower lobes, in their posterior segments, and they roughly correspond to the initial infected area.

In sepsis or trauma-induced ARDS, infiltrates are usually more patchy and diffuse. The posterior and basal segments are always more affected, but the distribution is even less homogeneous.

Loss of aeration also causes important changes in lung mechanical properties. These alterations are fundamental in the process of inflammation amplification and progression to ARDS in mechanically ventilated patients.

## Mechanical stress

Mechanical ventilation is an essential part of the treatment of ARDS. As loss of aeration (and the underlying disease) progress, the end tidal volume eventually grows to a level incompatible with life. Thus, mechanical ventilation is initiated to relieve respiratory muscles of their work, and to protect the usually obtunded patient's airways.

However, mechanical ventilation may constitute a risk factor for the development, or the worsening, of ARDS.

Aside from the infectious complications arising from invasive ventilation with tracheal intubation, positive-pressure ventilation directly alters lung mechanics during ARDS. The result is higher mortality, i.e. through baro-trauma, when these techniques are used.

In 1998, Amato *et al.* published a paper showing substantial improvement in the outcome of patients ventilated with lower tidal volumes ( $V_t$ ) ( $6 \text{ mL}\cdot\text{kg}^{-1}$ ). This result was confirmed in a 2000 study sponsored by the NIH. Although both these studies were widely criticized for several reasons, and although the authors were not the first to experiment lower-volume ventilation, they shed new light on the relationship between mechanical ventilation and ARDS.

One opinion is that the forces applied to the lung by the ventilator may work as a lever to induce further damage to lung parenchyma. It appears that shear stress at the interface between collapsed and aerated units may result in the breakdown of aerated units, which inflate asymmetrically due to the 'stickiness' of surrounding flooded alveoli. The fewer such interfaces around an alveolus, the lesser the stress.

Indeed, even relatively low stress forces may induce signal transduction systems at the cellular level, thus inducing the release of inflammatory mediators.

This form of stress is thought to be applied by the transpulmonary pressure (gradient) ( $P_1$ ) generated by the ventilator or, better, its cyclical variations. The better outcome obtained in patients ventilated with lower  $V_t$  may be interpreted as a beneficial effect of the lower  $P_1$ . Transpulmonary pressure, is an indirect function of the  $V_t$  setting on the ventilator, and only trial patients with plateau pressures (a surrogate for the actual  $P_1$ ) were less than 32 cmH<sub>2</sub>O (3.1 kPa) had improved survival.

The way  $P_1$  is applied on alveolar surface determines the shear stress to which lung units are exposed. ARDS is characterized by a usually inhomogeneous reduction of the airspace, and thus by a tendency towards higher  $P_1$  at the same  $V_t$ , and towards *higher* stress on *less* diseased units.

The inhomogeneity of alveoli at different stages of disease is further increased by the gravitational gradient to which they are exposed, and the different perfusion pressures at which blood flows through them. Finally, abdominal pressure exerts an additional pressure on inferoposterior lung segments, favoring compression and collapse of those units.

The different mechanical properties of alveoli in ARDS may be interpreted as having varying *time constants* (the product of alveolar compliance  $\times$  resistance). A long time constant indicates an alveolus which opens slowly during tidal inflation, as a consequence of contrasting pressure around it, or altered water-air interface inside it (loss of surfactant, flooding).

Slow alveoli are said to be 'kept open' using positive end-expiratory pressure, a feature of modern ventilators which maintains a positive airway pressure throughout the whole respiratory cycle. A higher mean pressure cycle-wide slows the collapse of diseased units, but it has to be weighed against the corresponding elevation in  $P_1$ /plateau pressure. Newer ventilatory approaches attempt to maximize mean airway pressure for its ability to 'recruit' collapsed lung units while minimizing the shear stress caused by frequent openings and closings of aerated units.

The prone position also reduces the inhomogeneity in alveolar time constants induced by gravity and edema. If clinically appropriate, mobilization of the ventilated patient can assist in achieving the same goal.

## **Progression**

If the underlying disease or injurious factor is not removed, the amount of inflammatory mediators released by the lungs in ARDS may result in a systemic inflammatory response syndrome (or sepsis if there is lung infection). The evolution towards shock and/or multiple organ failure follows paths analogous to the pathophysiology of sepsis.

This adds up to the impaired oxygenation which is the central problem of ARDS, as well as to respiratory acidosis, which is often caused by ventilation techniques such as permissive hypercapnia which attempt to limit ventilator-induced lung injury in ARDS.

The result is a critical illness in which the 'endothelial disease' of severe sepsis/SIRS is worsened by the pulmonary dysfunction, which further impairs oxygen delivery.

## **Treatment**

### **General**

Acute respiratory distress syndrome is usually treated with mechanical ventilation in the Intensive Care Unit. Ventilation is usually delivered through oro-tracheal intubation, or tracheostomy whenever prolonged ventilation ( $\geq 2$  weeks) is deemed inevitable.

The possibilities of non-invasive ventilation are limited to the very early period of the disease or, better, to prevention in individuals at risk for the development of the disease (atypical pneumonias, pulmonary contusion, major surgery patients).

Treatment of the underlying cause is imperative, as it tends to maintain the ARDS picture.

Appropriate antibiotic therapy must be administered as soon as microbiological culture results are available. Empirical therapy *may* be appropriate if local microbiological surveillance is efficient. More than 60% ARDS patients experience a (nosocomial) pulmonary infection either before or after the onset of lung injury.

The origin of infection, when surgically treatable, must be operated on. When sepsis is diagnosed, appropriate local protocols should be enacted.

Commonly used supportive therapy includes particular techniques of mechanical ventilation and pharmacological agents whose effectiveness with respect to the outcome has not yet been proven. It is now debated whether mechanical ventilation is to be considered mere supportive therapy or actual treatment, since it may substantially affect survival.

## **Mechanical ventilation**

The overall goal is to maintain acceptable gas exchange and to minimize adverse effects in its application. Three parameters are used: PEEP (positive end-expiratory pressure, to maintain maximal recruitment of alveolar units), mean airway pressure (to promote recruitment and predictor of hemodynamic effects) and plateau pressure (best predictor of alveolar overdistention).

Conventional therapy aimed at tidal volumes ( $V_t$ ) of 12-15 ml/kg. Recent studies have shown that high tidal volumes can overstretch alveoli resulting in volutrauma (secondary lung injury). The ARDS Clinical Network, or ARDSNet, completed a landmark trial that showed improved mortality when ventilated with a tidal volume of 6 ml/kg compared to the traditional 12 ml/kg. Low tidal volumes ( $V_t$ ) may cause hypercapnia and atelectasis due to their inherent tendency to increase dead space.

Low tidal volume ventilation was the primary independent variable associated with reduced mortality in the NIH-sponsored ARDSnet trial of tidal volume in ARDS. Plateau pressure less than 30 cm H<sub>2</sub>O was a secondary goal, and subsequent analyses of the data from the ARDSnet trial (as well as other experimental data) demonstrate that there appears to be NO safe upper limit to plateau pressure; that is, regardless of plateau pressure, patients fare better with low tidal volumes.

## **APRV (Airway Pressure Release Ventilation) and ARDS / ALI**

No particular ventilator mode is known to improve mortality in ARDS. The landmark ARDSNet trial used a volume controlled mode and showed decreased mortality with smaller volumes. However, other modes of ventilation have not been directly compared to volume controlled ventilation.

Some practitioners favor airway pressure release ventilation (APRV). Advantages to APRV ventilation are alleged to include: decreased airway pressures, decreased minute ventilation, decreased dead-space ventilation, promotion of spontaneous breathing, almost 24 hour a day alveolar recruitment, decreased use of sedation, near elimination of neuromuscular blockade, optimized arterial blood gas results, mechanical restoration of FRC (functional residual capacity), a positive effect on cardiac output (due to the negative inflection from the elevated baseline with each spontaneous breath), increased

organ and tissue perfusion, potential for increased urine output secondary to increased renal perfusion.

None of these putative advantages have been shown to translate to better outcomes for patients with ARDS in large, randomized, multicenter trials

The main disadvantage of APRV is that it is in some ways exactly opposite of the low tidal volume ventilation strategy that was demonstrated to be effective in the ARDSNet trial. In that trial, a strategy of low tidal volumes was found to be beneficial compared to high tidal volumes. APRV is, in essence, low frequency, very high volume ventilation. All theoretical justifications pale in comparison to data that suggest that low alveolar pressures and hence low volumes benefit patients with ARDS.

A study is needed to evaluate whether APRV will reduce patient mortality when compared to the ARDSNet protocol.

### **Positive end-expiratory pressure**

Positive end-expiratory pressure (PEEP) is used in mechanically-ventilated patients with ARDS to improve oxygenation. In ARDS, three populations of alveoli can be distinguished. There are normal alveoli which are always inflated and engaging in gas exchange, flooded alveoli which can never, under any ventilatory regime, be used for gas exchange, and atelectatic or partially flooded alveoli that can be "recruited" to participate in gas exchange under certain ventilatory regimes. The recruitable alveoli represent a continuous population, some of which can be recruited with minimal PEEP, and others which can only be recruited with high levels of PEEP. An additional complication is that some or perhaps most alveoli can only be opened with higher airway pressures than are needed to keep them open. Hence the justification for maneuvers where PEEP is increased to very high levels for seconds to minutes before dropping the PEEP to a lower level. Finally, PEEP can be harmful. High PEEP necessarily increases mean airway pressure and alveolar pressure. This in turn can damage normal alveoli by overdistension resulting in DAD.

The 'best PEEP' used to be defined as 'some' cmH<sub>2</sub>O above the lower inflection point (LIP) in the sigmoidal pressure-volume relationship curve of the lung. Recent research has shown that the LIP-point pressure is no better than any pressure above it, as recruitment of collapsed alveoli, and more importantly the overdistension of aerated units, occur throughout the whole inflation. Despite the awkwardness of most procedures used to trace the pressure-volume curve, it is still used by some to define the *minimum* PEEP to be applied to their patients. Some of the newest ventilators have the ability to automatically plot a pressure-volume curve. The possibility of having an 'instantaneous' tracing trigger might produce renewed interest in this analysis.

PEEP may also be set empirically. Some authors suggest performing a 'recruiting maneuver' (i.e., a short time at a very high continuous positive airway pressure, such as 50 cmH<sub>2</sub>O (4.9 kPa), to recruit, or open, collapsed units with a high distending pressure)

before restoring previous ventilation. The final PEEP level should be the one just before the drop in PaO<sub>2</sub> (or peripheral blood oxygen saturation) during a step-down trial.

Intrinsic PEEP (iPEEP), or auto-PEEP, first described by John Marini of St. Paul Regions Hospital, is a potentially unrecognized contributor to PEEP in patients. When ventilating at high frequencies, its contribution can be substantial, particularly in patients with obstructive lung disease. iPEEP has been measured in very few formal studies on ventilation in ARDS patients, and its contribution is largely unknown. Its measurement is recommended in the treatment of ARDS patients, especially when using high-frequency (oscillatory/jet) ventilation.

A compromise between the beneficial and adverse effects of PEEP is inevitable.

### **Prone position**

Distribution of lung infiltrates in acute respiratory distress syndrome is non-uniform. Repositioning into the prone position (face down) might improve oxygenation by relieving atelectasis and improving perfusion. However, although the hypoxemia is overcome there seems to be no effect on overall survival.

### **Fluid management**

Several studies have shown that pulmonary function and outcome are better in patients that lost weight or pulmonary wedge pressure was lowered by diuresis or fluid restriction.

### **Corticosteroids**

A Meduri et al. study has found significant improvement in ARDS using modest doses of corticosteroids. The initial regimen consists of methylprednisolone 2 mg/kg daily. After 3–5 days a response must be apparent. In 1–2 weeks the dose can be tapered to methylprednisolone 0.5-1.0 mg daily. Patients with ARDS do not benefit from high-dose corticosteroids. This was a study involving a small number of patients in one center. A recent NIH-sponsored multicenter ARDSnet LAZARUS study of corticosteroids for ARDS demonstrated that they are not efficacious in ARDS.

### **Nitric oxide**

Inhaled nitric oxide (NO) potentially acts as selective pulmonary vasodilator. Rapid binding to hemoglobin prevents systemic effects. It should increase perfusion of better ventilated areas. There are no large studies demonstrating positive results. Therefore its use must be considered individually.

Almitrine bismesylate stimulates chemoreceptors in carotic and aortic bodies. It has been used to potentiate the effect of NO, presumably by potentiating hypoxia-induced pulmonary vasoconstriction. In case of ARDS it is not known whether this combination is useful.

## **Surfactant therapy**

To date no prospective controlled clinical trial has shown a significant mortality benefit of exogenous surfactant in ARDS.

## **Complications**

Since ARDS is an extremely serious condition which requires invasive forms of therapy it is not without risk. Complications to be considered are:

- Pulmonary: barotrauma (volutrauma), pulmonary embolism (PE), pulmonary fibrosis, ventilator-associated pneumonia (VAP).
- Gastrointestinal: hemorrhage (ulcer), dysmotility, pneumoperitoneum, bacterial translocation.
- Cardiac: arrhythmias, myocardial dysfunction.
- Renal: acute renal failure (ARF), positive fluid balance.
- Mechanical: vascular injury, pneumothorax (by placing pulmonary artery catheter), tracheal injury/stenosis (result of intubation and/or irritation by endotracheal tube).
- Nutritional: malnutrition (catabolic state), electrolyte deficiency.

## **Epidemiology**

The annual incidence of ARDS is 1.5–13.5 people per 100,000 in the general population. Its incidence in the intensive care unit (ICU), mechanically ventilated population is much higher. Brun-Buisson *et al.* (2004) reported a prevalence of acute lung injury (ALI) of 16.1% percent in ventilated patients admitted for more than 4 hours. More than half these patients may develop ARDS.

Mechanical ventilation, sepsis, pneumonia, shock, aspiration, trauma (especially pulmonary contusion), major surgery, massive transfusions, smoke inhalation, drug reaction or overdose, fat emboli and reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy may all trigger ARDS. Pneumonia and sepsis are the most common triggers, and pneumonia is present in up to 60% of patients. Pneumonia and sepsis may be either causes or complications of ARDS.

Elevated abdominal pressure of any cause is also probably a risk factor for the development of ARDS, particularly during mechanical ventilation.

The mortality rate varies from 30% to 85%. Usually, randomized controlled trials in the literature show lower death rates, both in control and treatment patients. This is thought to be due to stricter enrollment criteria. Observational studies generally report 50%–60% mortality.