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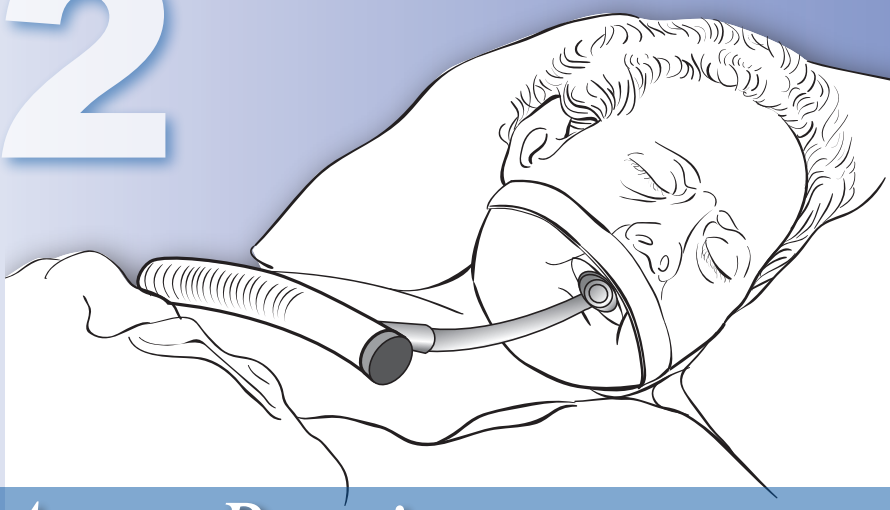


Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a condition in which the lungs suffer severe widespread injury, interfering with their ability to take up oxygen. A low blood oxygen level and the inability to get oxygen to normal levels is the hallmark of ARDS. The term *acute* reflects the sudden onset—over minutes or hours—of an injury. Acute lung injury (ALI) is a more recently coined term that includes ARDS but also milder degrees of lung injury. ALI and ARDS always result from another severe underlying disease. The range of diseases causing ARDS is broad, and they may also damage organs other than the lungs, but the lung injury usually dominates the clinical picture (1).

The term *acute respiratory distress syndrome* was coined in 1967, with similar lung injury being recognized in both medical and surgical patients. About this same time, the condition was being widely recognized in severely wounded soldiers in the Vietnam War. The name was chosen in part to reflect similarities to the previously described infant respiratory distress syndrome in premature infants.

Although ARDS has undoubtedly always occurred, it has only been recognized in the modern medical era because more severely and acutely ill patients now survive long enough to develop lung injury as a complication of their underlying severe disease.

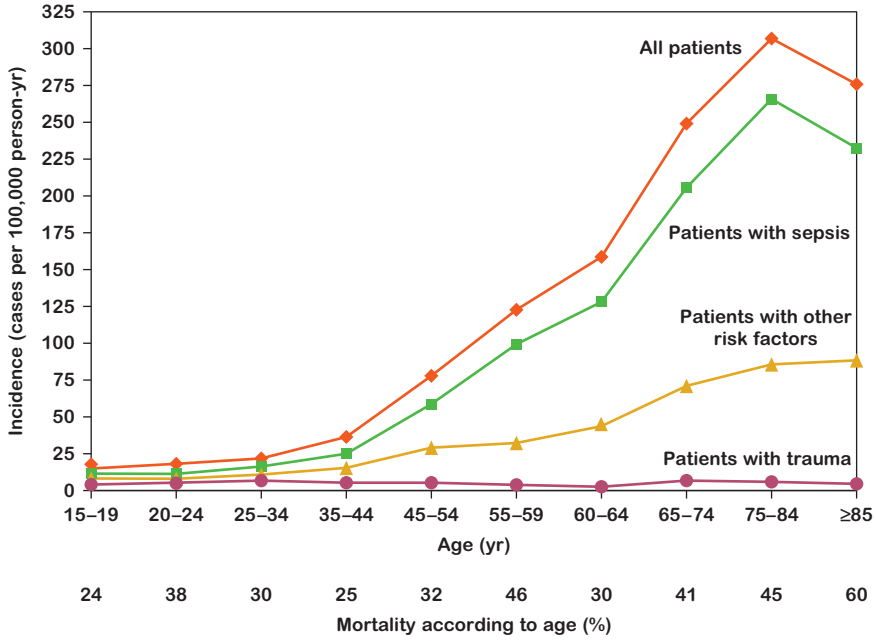
Whom does it affect?

Epidemiology, prevalence, economic burden, vulnerable populations

The occurrence of ARDS depends on several factors. Infectious diseases, which can result in ARDS, vary widely by geographic region. For example, malaria is the most frequent cause of ARDS in some parts of the world but does not exist in most of North America.

People at risk for ARDS are those with or at risk for the underlying diseases associated with the syndrome. The most common of these is sepsis, a severe infection that spreads throughout the body via the bloodstream. Victims of trauma and those who aspirate stomach contents into the lung are also at high risk for ARDS. A less common cause of direct injury is the inhalation of high concentrations of toxic gases, which can occur with severe smoke inhalation and in industrial accidents.

Age- and risk-specific incidence of mortality from acute lung injury



Sepsis is the most common condition leading to acute lung injury or acute respiratory distress syndrome. Mortality from both conditions is high and increases with age (2).

CASE STUDY

A 33-year-old woman developed back pain that worsened over several days. She took several medications, but the pain did not abate. After five days, she developed breathlessness and was hospitalized. The next day her blood pressure dropped and her kidneys failed. The following day, her breathing deteriorated and she required mechanical ventilation. Breathing became more difficult, and the high pressure required by the ventilator to get air into her lungs ruptured the lung alveoli, causing air to escape the lungs and be trapped inside the chest (pneumothorax). This was treated with a tube through the chest wall to allow the lungs to expand. She was deeply sedated to reduce the work required by her respiratory muscles. She developed pneumonia, and, after about three weeks on the ventilator, a new breathing tube was placed directly into the trachea (tracheostomy) in preparation for long-term mechanical ventilation. Fortunately, her kidney function returned, and she was able to clear the fluid in her lungs. Antibiotics treated the pneumonia. After four weeks in the hospital, the sedation was stopped, and after nine weeks, the tracheostomy tube was removed.

Comment

The woman, as most patients with ARDS who spend a prolonged time on a mechanical ventilator, did not recall much of the hospitalization. She remembered the rapidity with which she became ill and that several times she thought she was dying. For two years, she suffered from a form of post-traumatic stress disorder with flashbacks, but the flashbacks eventually stopped.

A recent study of Washington state's King County reflects the prevalence of acute lung injury and ARDS in North America. All patients with these conditions were identified in all hospitals of the county, a mixed urban and rural population that includes the city of Seattle. Seventy-nine people per 100,000 population per year developed ALI, and 59 of these met the criteria for the more severe form of ARDS. The death rate of ALI patients was 38.5 percent. Using the U.S. census and assuming the same frequency throughout the country, 190,600 people per year develop ALI, and 74,500 die of, or with, the disease in the United States. This makes ALI and ARDS diseases with major consequences to public health, causing about twice as many deaths per year as breast cancer or prostate

cancer and several times more than HIV/AIDS (2). Yet, the general public is largely unaware of these common diseases.

What we are learning about the disease

Pathophysiology, causes: genetic, environment, microbes

The cause of the acute lung injury can be either direct, with the injurious agent reaching the lung through the airways or by trauma to the chest, or indirect, with the injurious agent arriving at the lungs through the bloodstream. The affected areas in ARDS are the alveoli (air sacs), where oxygen enters the blood and carbon dioxide leaves it (gas exchange). The thin wall between the blood and air is made up of the blood capillary and the alveolar wall (alveolar-capillary membrane). The alveolar-capillary membrane is extremely delicate, less than 0.5 micrometers in width at its thinnest segment where gas exchange takes place. (For comparison, an average human hair is about 100 micrometers in width.) In ARDS, both the capillary and alveolar cells are injured, whether the initiating process is direct or indirect. Injury to this membrane allows fluid to spill into the lung, thus hindering or preventing gas exchange.

The aspiration of stomach contents into the lung or the inhalation of toxic gases are examples of direct injury causing ARDS. Indirect lung injury, however, is a more common cause of ARDS and is usually associated with severe infections or severe trauma. Regardless of the initiating event, an inflammatory chain reaction is set off. Molecules released by infected or injured cells signal white cells from the blood to enter the affected area. The incoming white blood cells combine with resident cells to produce more chemicals (called *cytokines* and *chemokines*), which induce a variety of actions involved in the inflammatory process. Inflammation is usually beneficial, in that it promotes killing and containment of infectious agents and clearing of the debris created by the infection or injury. Occasionally, however, exuberant inflammation can spread beyond the originally damaged organ via the bloodstream to injure other organs and tissues at distant sites. This systemic process is called *sepsis* when the initiating insult is an infection, but a similar, if not identical, process can occur when the original insult is traumatic injury.

Sepsis or sepsis-like syndromes can cause injury and failure of many organs. When they affect the lungs, they most commonly cause ARDS. In patients with sepsis or sepsis-like syndromes, the lungs are often the first organ to be injured. They are often the most severely injured organ, and they frequently represent the

only organ failure that is recognized clinically. This association may be because the lungs are the only organ to receive all the blood of the body. Although all the blood flows through the chambers of the heart, only a fraction of the blood supplies the heart tissues themselves. Thus the lungs receive the full brunt of the injurious cytokines and other molecules. The leakage of fluid through the alveolar-capillary membrane and flooding of alveoli interferes with oxygenation and causes shortness of breath and respiratory distress. The excess alveolar fluid mixes with the normal lung surfactant and can destabilize the alveoli, allowing them to collapse and thus not be available for breathing.

The microbes causing sepsis leading to ARDS vary widely in type and geographic distribution. In developed countries, bacterial infections are the most common, often with organisms partially or highly resistant to antibiotics that are common in hospital environments. Viruses that cause pneumonias can cause ARDS. In fact, most of the deaths in the severe acute respiratory syndrome (SARS) and H1N1 influenza epidemics were due to ARDS.

How is it prevented, treated, and managed?

Prevention, treatment, staying healthy, prognosis

Prevention of ARDS can be accomplished by preventing the infections and injuries that cause it. Even if trauma or infection cannot be prevented, early aggressive treatment may avert ARDS. Promptly hydrating persons in shock or administering antibiotics to persons with pneumonia may correct the underlying process enough to prevent ARDS from developing.

Once ARDS develops, the management of these patients consists of appropriate treatment of the underlying or causative illness, excellent supportive care, and prevention of complications. Appropriate treatment of an underlying infection is particularly important and consists of identifying the causative organism as best as possible and draining any abscesses, as well as giving antibiotics.

The care of the critically ill patient is highly complex because of the severity of the patient's illness, the combination of diseases and organ failures and their interactions, and the rapidity of changes in the patient's condition.

Mechanical ventilation is a key component of good supportive care. The ventilator must be set to deliver enough air to make sure the patient's oxygen level is adequate. Positive end-expiratory pressure (PEEP) is applied to each breath to keep alveoli open, and a host of other adjustments are made to keep

Steve Schneider

An intensive care unit is a busy and complicated place, where patients are comprehensively monitored, and interventions take place quickly. Improvements in how patients are cared for in these units are quite likely to be responsible for the better outcomes in acute respiratory distress syndrome

the patient alive without causing harm to the lungs or the rest of the body. The use of small breaths from the ventilator avoids further injury and is particularly important.

Fluid management is complex in ARDS because the lungs are flooding while the patient often does not have enough blood volume to maintain an adequate blood pressure. Although sedative and pain relief medications are essential, too much sedation can keep the patient on the ventilator longer than necessary and cause delirium and lack of cooperation. Medicines that are eliminated by the liver or kidney may accumulate and interact if these organs are dysfunctional. Other treatments may also cause harm. The mere presence of a tube in the trachea to deliver the ventilation is associated with increased risk of pneumonia. One of the goals is also to reduce patient discomfort related to the tubes, blood drawing, alarms, and frequent nursing checks.

A critical decision for an improving patient is when to remove the mechanical ventilation. The longer a patient remains on the ventilator, the greater the chance of complications, including airway injury from the tube and pneumonia. Once the patient's ventilation requirements have decreased to a predetermined

level, the patient is given a daily trial of breathing on his or her own (spontaneous breathing trial) to see if breathing can comfortably continue and adequate oxygenation can be maintained.

The death rate associated with ARDS is high, with overall mortality between 30 and 40 percent. Once a patient survives the acute episode of ARDS, his or her lung function gradually improves over the next six months to a year, with eventual return to normal or near-normal lung function in nearly all cases. An occasional patient is left with significant scarring and lower than normal lung volumes.

Despite normal lung function in nearly all survivors, in self-assessments, these patients frequently rate their quality of life as impaired. Recent studies of ARDS survivors have found psychological problems, including higher than expected rates of depression and post-traumatic stress disorder, neurocognitive problems that are usually relatively mild in degree and improve over years, and neuromuscular weakness. The causes of these problems and how best to prevent and treat them are subjects of intense research interest.

Are we making a difference?

Research past, present, and future

Although the mortality related to ARDS is high, it has substantially improved in recent years. This decline in the death rate started before any specific treatment had been shown to be beneficial for ARDS and was likely related to improvements in critical care medicine and management of these patients.

A great deal has been learned about the inflammatory process and how fluids are handled in the lung, but inflammation is a highly complex process, with new molecules and pathways—and their cellular interactions—being discovered regularly. Several trials have tested intervention in the inflammatory process, but none have shown substantial benefit.

Considerable interest exists in whether genetic makeup affects the development of ARDS, but the research in this area is in its early stages. Some gene mutations have been shown to be associated with an increased risk of ARDS development, but for the overwhelming majority of cases of ARDS, no specific genetic profile has been identified. Interest remains high because of the clinical observation that while two patients may share similar characteristics and have the same disease, one may develop ARDS and the other may not.

Life-saving mechanical ventilation can itself result in further injury to the already-injured lungs of patients with ARDS. At times this ventilator-induced lung injury can result in worse and more permanent damage than that produced by ARDS itself. The National Institutes of Health sponsored the ARDS Clinical Network (commonly called *ARDSnet*) to carry out studies on patients with ARDS in the intensive care unit (ICU). One study published in 2000 showed that patients given smaller ventilator breaths had significantly higher survival than patients with conventional treatment (3). It also showed that the use of large breaths resulted in ongoing inflammation that traveled beyond the lungs. New modes of "lung protective ventilation" have been developed. The value of PEEP has been established in several studies, although determining the best level of PEEP for an individual patient remains an elusive goal.

Studies have shown that daily spontaneous breathing trials (without the ventilator's help) resulted in fewer days on the ventilator. To do the trials, it was necessary to stop sedation, which has also been shown to be beneficial. A simple method to help minimize aspiration and reduce the risk of developing pneumonia is to raise the head of the bed to between 30 and 45 degrees.

An ARDSnet study of ICU patients showed that a more conservative fluid administration strategy—initiated after adequate fluid intake was ensured—resulted in less time on mechanical ventilation and less time in the ICU. Other advances are being made and are tied closely to the management of patients in the intensive care unit.

What we need to cure or eliminate ARDS

Although it is not realistic to speak of cure when considering a form of injury, the two factors most likely to reduce the burden of ARDS are continued improvement in the care of patients in the ICU and breakthroughs in the understanding of the inflammatory process that result in new therapies. Technologies to better monitor and treat ARDS patients and evaluation of current procedures have resulted in past gains and are likely to continue to steadily increase patient care outcome. Gains from understanding the inflammatory process are long-term goals that are likely to help treat patients with ARDS and with many other diseases in which inflammation plays a part.

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3. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.

Web sites of interest

National Heart, Lung, and Blood Institute
www.nhlbi.nih.gov/health/dci/Diseases/Ards/Ards_WhatIs.html

ARDS Foundation
www.ardsil.com

ARDS Support Center
www.ards.org

National Heart, Lung, and Blood Institute ARDS Network (ARDSNet)
www.ardsnet.org