Pathophysiology (Process of the Disease) of HPAI H5N1 Avian Influenza

H5N1 is a subtype of influenza A virus that causes a highly infectious, severe respiratory disease in birds. Because the H5N1 is so deadly to poultry, it is classified as highly pathogenic avian influenza (HPAI). "Highly pathogenic" refers to the virus's ability to produce serious illness. As a variant of avian influenza (bird flu), it is this highly pathogenic strain that has caused serious outbreaks in domestic poultry in parts of Asia and the Middle East. As stated earlier in the previous section, the H5N1 was first discovered at Qinghai Lake in China, in 2005. It was at Qinghai Lake that the H5N1 spread to other migratory birds and has now been found in birds across the world.

The HPAI H5N1 is in many bird populations, especially in Southeast Asia. After first appearing in Asia, the strain is spreading globally. It is killing tens of millions of birds and causing the culling of hundreds of millions of others to prevent its spread. Most references to "bird flu" in the popular media refer to this strain.

H5N1 Human Infection

Although this influenza A virus is considered an avian disease, it can cause illness in humans and many other animal species. It is one of the few avian influenza viruses to have crossed the species barrier to infect humans, and it is the deadliest of those that have crossed the barrier. Most cases in humans have resulted from contact with infected poultry or surfaces contaminated with secretions/excretions from infected birds.

As of May 9, 2016, 850 cases of human infections with highly pathogenic H5N1 viruses have been reported to the World Health Organization (WHO) by sixteen countries in Asia, Africa, the Pacific, Europe, and the Near East. 449 of these people have died from their illness, approximately 60%. Egypt, Indonesia, and Viet Nam have reported the highest number of human HPAI H5N1 cases to date (WHO, 2016).[i] The majority of human infections of HPAI H5N1 have occurred among children and adults younger than 40 years old. Mortality has been highest in people aged 10-19 years old and in young adults (CDC, 2016). [ii]

At this time there is some evidence of limited human-to-human transmission of this virus. Research shows that when influenza viruses infect birds, the hemagglutinin surface protein of the virus is activated by acid in the entry pathway inside the host cell, enabling it to invade that cell. This is significant because the upper airways of the nasal cavities of mammals are more acidic than infected tissues of birds. Therefore, the H5N1 does not have the same effect on avian tissue as it does on mammalian tissue. What might infect but not kill ducks is highly lethal to mammals. As researchers work with this strain, they have determined that it would take only one mutation to render the hemagglutinin protein more adaptable to acid and change this avian virus to a human virus.

In January 2014, Canada had reported the first case of human infection with avian influenza A (H5N1) virus ever detected in the Americas. According to Canadian health officials, the patient, who died on January 3, 2014, had recently traveled to Beijing, China, where avian influenza A H5N1 is endemic among poultry. This was the first detected case of human infection with avian influenza A H5N1 virus in North or South America. It also was the first case of H5N1 infection ever imported by a traveler into a country where this virus is not present in poultry.

Thus far H5N1 remains an avian virus that has not changed substantially since its emergence; human infections remain rare and sporadic. Only one cluster was detected in 2012. Most human cases of H5N1 virus infection are due to exposure through direct or indirect contact with household/backyard poultry or contaminated environments, as opposed to contact with commercial poultry or wild birds. However, the risk still remains of human infection where the virus is circulating in poultry and to people who are exposed to infected birds.

H5N1 and the Lower Respiratory Tract

The attachment of all influenza A virus strains to cells requires sialic acids. This refers to a group of acids that are attached to virtually all animal cells. Some are very tissue sensitive and can be found in only very specific cells. There are a number of chemically different forms of sialic acids, and influenza virus strains vary in their affinity to them. These differences may determine which animal species can be infected.

Avian influenza virus strains preferentially bind to sialic acids on epithelial cells lining the gastrointestinal tract of a duck. Human influenza virus, however, prefer the sialic acids on human respiratory epithelial cells found in the lower respiratory tract. Research has proven that the H5N1 avian virus prefers this type of sialic acid. This explains why it causes acute lower respiratory tract disease in humans and severe viral pneumonia.

H5N1 and the Lower Respiratory Tract
Sebastian Kaulitzki/Shutterstock.com [iii]

Due to the fact that these viruses are not present in the upper respiratory airway, it is not readily spread with sneezes. This also provides a rational explanation for why H5N1 viruses, at present, rarely infect and spread between humans – although they can replicate efficiently in the lungs.

Pathophysiology of H5N1 Influenza

The results of a study done by scientists in Hong Kong were published and made accessible online in 2005. The conclusion showed that the H5N1 strain of virus can trigger inflammatory proteins called *cytokines* to reach levels of more than ten times higher than in the common human flu virus H1N1. This inflammation can cause damage to a patient's lungs to the extent that they are unable to breathe.

In order to explain the effect of these cytokines, we must first discuss the immune system. The immune system consists of specialized cells and organs and is the body's way of protecting itself from outside biological effects. It is divided into two sections: *innate immunity* and *adaptive immunity*.

Innate immune defense is general and nonspecific. It protects against many types of pathogens (microorganisms that can cause disease) and functions the same way regardless of the type or the number of times the same pathogen invades.

The adaptive immune response, on the other hand, is very precise in targeting certain pathogens. These responses are carried out by specialized white blood cells called lymphocytes consisting of both T cells and B cells. These cells recognize foreign molecules by their antigens and react against them. T cells attach to foreign cells with unfamiliar antigens, such as the hemagglutinins and neuraminidases found on influenza viruses. The T cells interact directly with the antigens and destroy them. B cells respond indirectly by producing antibodies. An *antibody* is a protein produced in response to a specific antigen that combines with that antigen to neutralize, inhibit or destroy it.

During the immune response to these antigens, cytokines are released. Cytokines are protein hormone like substances that act as messenger molecules and regulators in the immune system. In addition to carrying messages, they also behave as hormones and can produce effects on other cells close by. In short, cytokines promote an inflammatory response to infections. When there is an excessive amount of cytokines which can cause too much fluid to build up, this is called a *cytokine storm*. A cytokine storm describes an immune system that overreacts and damages the body causing multiple system organ failure.

In addition to a cytokine storm, the H5N1 virus is also able to destroy the immune process by its ability to disable the present immune system. It can even block the body's ability to build immunity against later infection by the same type of virus. During infection specific antibodies are produced to combat virus; however, infection of the H5N1 shows an absence of these antibodies, this suggests they are destroyed during the infection process

The Role of Cytokines and Avian Influenza

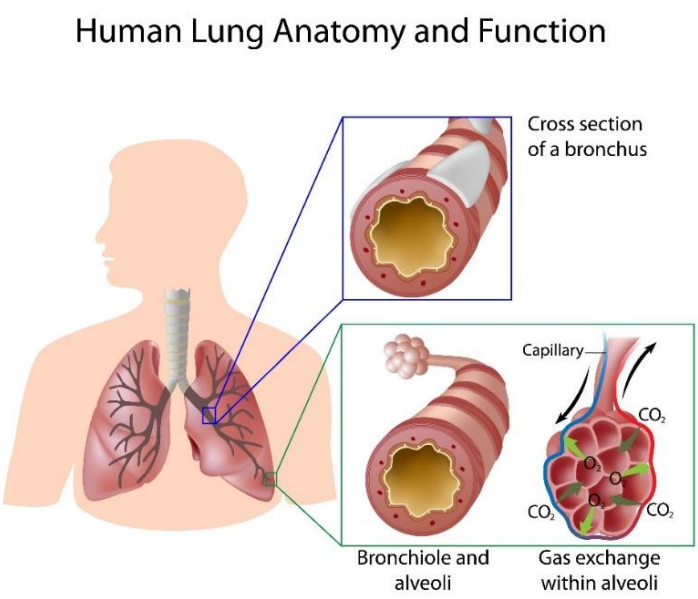
Since respiratory epithelial cells (cells that line the cavities in the body) are the primary target cell for replication of influenza viruses, it is pertinent to investigate the stimulation of cytokine production of H5N1 viruses in these particular cells.

Virtually all cells in the innate and adaptive immune systems produce cytokines. The secreted cytokines then bind to specific cytokine receptors on other cells of the immune system and influence their activity. They can either enhance certain responses to antigens or inhibit signals.

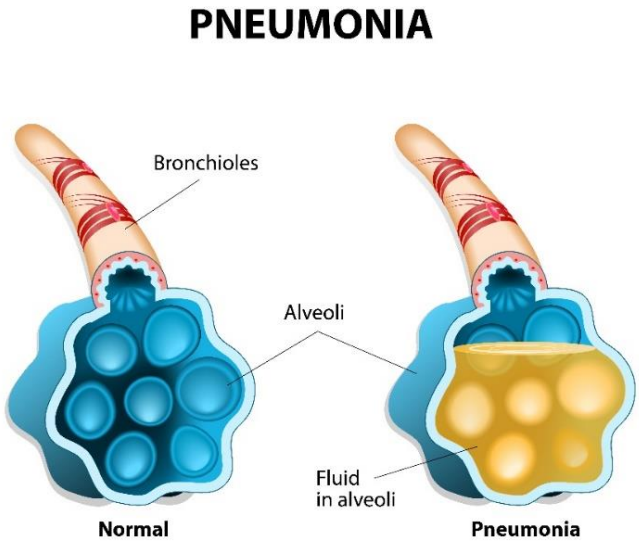
Cytokines that regulate innate immunity are produced primarily in response to pathogens (any agent that can cause disease). Most cytokines influence leukocytes and the endothelial cells (the layer of epithelial cells that form the inner lining of blood vessels and heart chambers) in order to promote and control inflammation.

Inflammation is a response of the immune system which brings large amounts of white blood cells to the injured or infected area to aid in the healing process. The white blood cells release chemicals, that includes cytokines, that increases the blood flow to the area. These chemicals induce inflammation which then causes fluids to leak out into the surrounding tissue. This results in swelling, redness, and increased warmth in the affected area. An example of this is the swelling of a joint after an injury.

Although cytokines help stimulate inflammation, they also contain regulatory components that inhibit over stimulation. The release of the inflammatory agent usually includes both inflammatory and ant-inflammatory signals. The H5N1 virus has outsmarted this process of our immune systems. It produces toxins that interfere with the control mechanisms of the immune system. The H5N1 is not only partially resistant to the cytokines that are involved in fighting viruses, but it also inhibits the production of anti-inflammatory cytokines. In other words, it causes a surge in the release of these inflammatory chemicals, and at the same time removes the control mechanisms to restrict their activity. The immune system basically goes out of control with no means of restraining it.



Alveoli and Gas Exchange
Alila Medical Media/Shutterstock.com [iv]



Fluid in Alveoli
Designua/Shutterstock.com[v]

When the H5N1 virus comes in contact with the cells of the trachea and alveoli in the lungs, it stimulates the production of cytokines. The cytokines then stimulate inflammation with increased fluids. This increase of fluids results in damaging the alveoli and lung tissue. The fluid buildup in the lungs known as pulmonary edema leads to difficulty breathing and acute respiratory distress syndrome (ARDS). The end stage result from a cytokine storm is sepsis and multiple organ dysfunction syndrome (MODS).

The increase of cytokine production is what sets avian flu apart from other influenzas. The hyper production of cytokines is very significant; it is why people experience severe illness with this virus as opposed to what is seen with other influenza viruses. The excessive production of cytokines is what leads to the death of those infected with the avian flu virus, by stimulating excessive inflammation thus causing the airways to become blocked. In addition to the H5N1, scientists believe this explains how the 1918 Influenza was so deadly, as well as the high death rate of the SARS outbreak in 2003.

Signs and Symptoms of H5N1 Influenza

Breathing difficulties develop about five days after the first symptoms leading to respiratory distress. A crackling sound develops upon inhalation, which is the air moving through the fluid building up in the alveoli. Almost all victims develop pneumonia. There is rapid deterioration, including multi-organ dysfunction and respiratory failure all within 3-5 days after symptom onset.

An average timeline for how the avian virus affects respiratory tissue in the following:

Day 1

- Severe bronchiolar and alveolar damage

Day 3-5

- Respiratory distress/failure

Day 7

- Hardly any viable lung tissue left to infect
- Still very strong viral replication

In a large number of patients, the H5N1 virus usually develops aggressively. The incubation period of two to eight days is longer than that of human seasonal flu which is two to three days. In some cases, the incubation period may take as long as 17 days. Incubation period is the amount of time between exposure to the disease and the development of signs and symptoms. For field investigations and monitoring of patient contacts, WHO (World Health Organization) recommends health care professionals use an incubation period of seven days.

Humans with avian flu may have the following signs and symptoms (many are similar to the seasonal human flu):

- A cough, usually dry
- A high fever, over 100.4 degrees F
- Aching bones, joints and muscles
- Bleeding from the nose
- Nasal congestion, and runny nose
- Chest pain
- Cold sweats and chills
- Fatigue
- Headache
- Loss of appetite, nausea
- Possible diarrhea
- Sleeping difficulties
- Bleeding from the gums
- Lower respiratory tract infection, which includes breathing difficulties
- Hoarse voice
- Sputum is sometimes bloody
- Tachycardia
- Hypotension

Patients with avian influenza can deteriorate rapidly, resulting in pneumonia, multiple organ failure, and death.

Diagnosing H5N1 Influenza

Avian influenza A virus infection in humans cannot be diagnosed by clinical signs and symptoms alone; laboratory testing is required. Avian influenza A virus infection is usually diagnosed by collecting a swab from the nose or throat of the sick person during the first few days of illness. This specimen is sent to a specialized lab set up with high levels of protection. There are approximately 140 designated laboratories of the Laboratory Response Network located in all 50 states of the United States of America.

Testing should be done when a patient has severe respiratory illness and clinical or epidemiological risk. Healthcare providers should contact their local or state health department as soon as possible to report any suspected human case of influenza H5N1 in the United States. Positive tests for influenza A H5N1 in the United States should be confirmed by Health and Human Services (HHS) and the Centers for Disease Control (CDC), which has been designated as a WHO H5 Reference laboratory.

Treatment Options of H5N1 Influenza

According to WHO antiviral medications, such as oseltamivir can suppress viral replication and improve outcomes for patients, especially survival prospects. Oseltamivir should be administered within 48 hours after the onset of symptoms for best effect. However, as avian influenza mortality rates are high, doctors may consider prescribing oseltamivir for patients who were diagnosed later. For those with severe symptoms, doctors may have to increase the recommended daily dose, as well as treatment duration. Physicians should bear in mind that drug absorption may be severely impaired in patients with severe gastrointestinal symptoms. Antiviral medications have no effect on a cytokine storm.

Patients diagnosed with avian flu or who are suspected of having avian flu will be told to either remain at home or will be hospitalized (in isolation from other patients).

Patients suspected or having been diagnosed with avian influenza should do the following:

- Rest
- Drink lots of fluids
- Receive proper nutrition
- Receive medications for pain and fever

Complications such as bacterial pneumonia are common in patients infected with H5N1 virus. These patients should be administered antibiotics; some may need extra oxygen.

Latest Research

Two research labs funded by National Institute of Health of the U.S. government have been in the news for creating mutations that enable the virus to be transmissible among mammals via airborne droplets. Thursday June 21, 2012, the long-awaited paper "Experimental Adaptation of an Influenza H5 HA Confers Respiratory Droplet Transmission to a Reassortant H5 HA/H1N1 Virus in Ferrets," was published. The results of the research were very enlightening.

It was determined that it only takes a handful of mutations for the virus to become airborne and easily transmitted from one animal to another. A second study shows those mutations not only can easily occur in nature – they have already started to do so. Through these studies they have determined that not only is a pandemic from this particular strain possible, but it is only a few mutations away from human-to-human transmission – and that it is inevitable.

When the results of this paper became known it was requested that the contents of this study not be published in order to keep such information from those who might use it maliciously. These labs and others around the world went on a voluntary moratorium to cease research in January 2012 that lasted one year. The halt was to give the scientists a chance to explain the research benefits and safety to the public, and to give governments and funding agencies a chance to review their policies.

On January 23, 2013, the moratorium lifted and scientists resumed work on their research. The controversy unfortunately still remains that the information could get into the wrong hands, and a strain could be developed for the use in a bioterrorist attack. There is also the risk of a lab accident.

There has been a surge of H5N1 cases during 2015, after reporting very few during the preceding two years. Most cases are due to the patients having contact with poultry, and no signs of human-to-human transmission have been reported. However, the cases have prompted speculation about whether the virus has changed in some way.

In response to this increase of cases, the United Nations Food and Agriculture Organizations (FAO) initiated a study to distinguish viruses circulating in Upper and Lower Egypt. Genetic sequencing revealed that the hemagglutinin genes in the virus continue to mutate but that all the samples are similar to those seen in previous years. However, the scientists also identified two mutations allowing enhanced receptor binding. The mutations have caused the avian virus to adapt and become more susceptible to binding with receptors found in humans. It was also determined that the H5N1 virus is only four mutations away from becoming a strain that would be human-to-human transmissible.

Scientists are concerned that the highly pathogenic H5N1 avian influenza virus one day could be able to sustain human-to-human transmission. Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population. If the highly pathogenic H5N1 avian influenza virus were to gain the capacity to sustain transmission from person-to-person, a pandemic could begin.

To date this strain has infected over 850 people approximately 60% of the cases have died. Indonesia, Egypt, Viet Nam, China, Cambodia, and Thailand are among several other nations that have reported deaths due to this strain. Vaccinating flocks of birds, regulating backyard poultry and bird markets, culling birds, and education have helped in keeping the H5N1 restrained in these countries. However, viruses mutate and reassort regularly and the H5N1 is no exception.

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[i]"Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO, 2003-2015", World Health Organization Website. Last modified May 9, 2016, accessed June 23, 2016. http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/.

[ii] "Highly Pathogenic Asian Avian Influenza A (H5N1) in People" Centers for Disease Control and Prevention, CDC Website, Last modified June 11, 2015, accessed June 23, 2016. http://www.cdc.gov/flu/avianflu/h5n1-people.htm.

[iii] Sebastian Kaulitzki/Shutterstock.com, http://www.shutterstock.com/pic-4275289.html

[iv] Alila Medical Media/Shutterstock.com, http://www.shutterstock.com/pic-96426923.html

[v] Designua/Shutterstock.com, http://www.shutterstock.com/pic-214353118.html