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SWINE FLU: AN OVERVIEW

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ABSTRACT

Swine flu (swine influenza) is a respiratory disease caused by viruses (influenza viruses belonging to family Orthomyxoviridae) that infect the respiratory tract of pigs and result in nasal secretions, a barking-like cough, decreased appetite, and listless behaviour. Oseltamivir (Tamiflu) and zanamivir (Relenza) is the recommended drug both for prophylaxis and treatment. The best treatment for influenza infections in humans is prevention by vaccination.

Key words: Swine flu, respiratory tract infection, H1N1 virus, influenza virus

INTRODUCTION

Swine flu (swine influenza) is a respiratory disease caused by viruses (influenza viruses) that infect the respiratory tract of pigs and result in nasal secretions, a barking-like cough, decreased appetite (Bouvier et al, 2008). A highly contagious form of influenza seen in swine, caused by a virus of the family Orthomyxoviridae (Kimura et al, 1997). The infection is communicable to humans and caused a worldwide epidemic in 1918. The H1N1 virus (swine flu) is a new flu virus strain that has caused a worldwide pandemic in humans from June 2009 to August 2010. The Centers for Disease Control and Prevention now call the virus 2009 H1N1, an acute and highly contagious respiratory disease of swine caused by the orthomyxo virus thought to be the same virus that caused the 1918 influenza pandemic an acute febrile highly contagious viral disease. A highly contagious form of human influenza caused by a filterable virus identical or related to a virus formerly isolated from infected swine. The respiratory infection popularly known as swine flu is caused by an influenza virus first recognized in spring 2009, near the end of the usual Northern Hemisphere flu season. The new virus, 2009 H1N1, spreads quickly and easily (Matsuzaki et al, 2002). A few months after the first cases were reported, rates of confirmed H1N1-related illness were increasing in almost all parts of the world. As a result, the World Health Organization declared the infection a global pandemic. That official designation remained in place for more than a year. Technically, the term "swine flu" refers to influenza in pigs. Occasionally, pigs transmit influenza viruses to people, mainly hog farm workers and veterinarians. (Lynch et al, 2007)

Symptoms of Swine Flu

Swine flu produces most of the same symptoms in pigs as human flu produces in people (Yassine HM, 2007) Swine flu can last about one to two weeks in pigs that survive. In a number of

instances, people have developed the swine flu infection when they are closely associated with pigs (for example, farmers, pork processors), and likewise, pig populations have occasionally been infected with the human flu infection. Investigators think the 2009 swine flu strain, first seen in Mexico, should be termed novel H1N1 flu since it is mainly found infecting people and exhibits two main surface antigens, H1 (hemagglutinin type 1) and N1 (neuraminidase type1). Recent investigations show the eight RNA strands from novel H1N1 flu have one strand derived from human flu strains, two from avian (bird) strains, and five from swine strains (Heinen P, 2003).

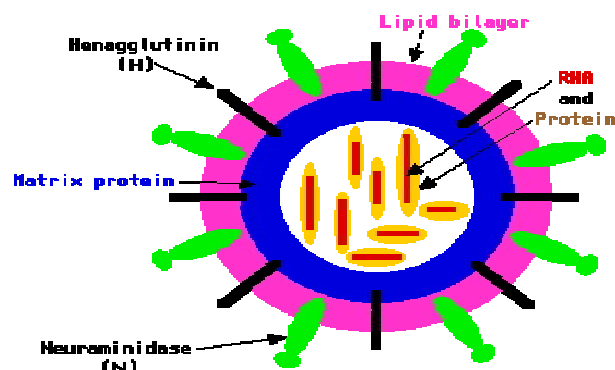


Fig 1. shows Influenza Virus (Gilchrist MJ, 2007)

Symptoms of swine flu infections include (Antonovics J, 2006):

- Fever, which is usually high, but unlike seasonal flu, is sometimes absent
- Cough
- Runny nose or stuffy nose
- Sore throat
- Body aches
- Headache
- Chills
- Fatigue or tiredness, which can be extreme
- Diarrhoea and vomiting, sometimes, but more commonly seen than with seasonal flu
- Signs of a more serious swine flu infection might include pneumonia and respiratory failure.

Serious Swine Flu Symptoms (Schmeck , Harold M. 1976)

More serious symptoms that would indicate that a child with swine flu would need urgent medical attention include:

- Fast breathing or trouble breathing
- Bluish or gray skin color
- Not drinking enough fluids
- Severe or persistent vomiting
- Not waking up or not interacting
- Being so irritable that the child does not want to be held
- Flu-like symptoms improve but then return with fever and worse cough
- Unusual tiredness
- Headache
- Runny nose
- Sore throat

- Shortness of breath or cough
- Loss of appetite
- Aching muscles

Swine Flu Symptoms vs. a Cold or Sinus Infection (Haber P et al, 2009)

It is important to keep in mind most children with a runny nose or cough will not have swine flu and will not have to see their pediatrician for swine flu testing.

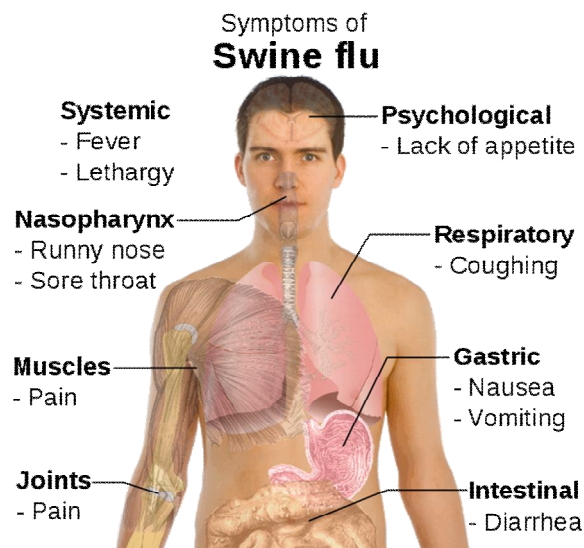


Fig 2. shows symptoms of swine Flu (Patterson KD, 1991)

High-risk groups (Vellozzi C,2009):

High Risk group includes persons having

- Chronic (long-term) lung disease
- Chronic heart disease
- Chronic kidney disease
- Chronic liver disease
- Chronic neurological disease (neurological disorders include chronic fatigue syndrome, multiple sclerosis and parkinson's disease)
- Immunosuppression (whether caused by disease or treatment)
- Diabetes mellitus

Also at risk are:

- Patients who have had drug treatment for asthma within the past three years
- Pregnant women
- People aged 65 and older (gaydos jc,2006)

PATHOPHYSIOLOGY OF SWINE FLU

First, the influenza viruses (types A, B, C) are enveloped RNA viruses with a segmented genome; this means the viral RNA genetic code is not a single strand of RNA but exists as eight different RNA segments in the influenza viruses. A human (or bird) influenza virus can infect a pig respiratory cell at the same time as a swine influenza virus; some of the replicating RNA

strands from the human virus can get mistakenly enclosed inside the enveloped swine influenza virus. For example, one cell could contain eight swine flu and eight human flu RNA segments. The total number of RNA types in one cell would be 16; four swine and four human flu RNA segments could be incorporated into one particle, making a viable eight RNA segmented flu virus from the 16 available segment types. Various combinations of RNA segments can result in a new subtype of virus (known as antigenic shift) that may have the ability to preferentially infect humans but still show characteristics unique to the swine influenza virus (Figure 3). It is even possible to include RNA strands from birds, swine, and human influenza viruses into one virus if a cell becomes infected with all three types of influenza (for example, two bird flu, three swine flu, and three human flu RNA segments to produce a viable eight-segment new type of flu viral genome). Formation of a new viral type is considered to be antigenic shift; small changes in an individual RNA segment in flu viruses are termed antigenic drift and result in minor changes in the virus. However, these can accumulate over time to produce enough minor changes that cumulatively change the virus antigenic makeup over time (usually years). Second, pigs can play a unique role as an intermediary host to new flu types because pig respiratory cells can be infected directly with bird, human, and other mammalian flu viruses. Consequently, pig respiratory cells are able to be infected with many types of flu and can function as a "mixing pot" for flu RNA segments (Figure 3). Bird flu viruses, which usually infect the gastrointestinal cells of many bird species, are shed in bird faeces. Pigs can pick these viruses up from the environment and seem to be the major way that bird flu virus RNA segments enter the mammalian flu virus population. (McKinney WP et al, 1990)

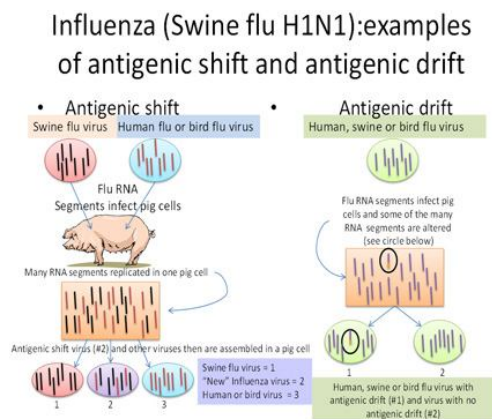


Fig 3. Shows Pathophysiology of Swine Flu (Heinen, P. (2003)

DIAGNOSIS (Gray GC, 2009)

- A quick test (for example, nasopharyngeal swab sample) is done to see if the patient is infected with influenza A or B virus. Most of the tests can distinguish between A and B types. The test can be negative (no flu infection) or positive for type B, the flu is not likely to be swine flu (H1N1). If it is positive for type A, the person could have a conventional flu strain or swine flu (H1N1). However, the accuracy of these tests has

been challenged, and the U.S. Centers For Disease Control and Prevention (CDC) has not completed their comparative studies of these tests, however, a new test developed by the CDC and a commercial company reportedly can detect H1N1 reliably in about one hour; as of October 2009, the test is only available to the military.

- Swine flu (H1N1) is definitively diagnosed by identifying the particular antigens associated with the virus type. In general, this test done in a specialized laboratory and is not done by many doctor's offices or hospital laboratories. However, doctor's offices are able to send specimens to specialize laboratories if necessary. Because of the larger number of novel H1N1 swine flu cases (as of October 2009, the vast majority of flu cases (about 99%) are due to novel H1N1 flu Viruses), the CDC recommends only hospitalizes patient's flu virus strains be sent to reference labs to be identified.

Treatment (Myers KP, 2006)

The guiding principles are:

Early implementation of infection control precautions to minimize

- nosocomial / household spread of disease
- Prompt treatment to prevent severe illness & death.
- Early identification and follow up of persons at risk.

1. Oseltamivir Medication

Oseltamivir is the recommended drug both for prophylaxis and treatment.

Dose for treatment is as follows:

By Weight:

- For weight <15kg 30 mg BD for 5 days
- 15-23kg 45 mg BD for 5 days
- 24-<40kg 60 mg BD for 5 days
- >40kg 75 mg BD for 5 days⁹³
- For infants:
 - < 3 months 12 mg BD for 5 days
 - 3-5 months 20 mg BD for 5 days
 - 6-11 months 25 mg BD for 5 days
- It is also available as syrup (12mg per ml)
- If needed dose & duration can be modified as per clinical condition. (Richard E, 1978)

Adverse reactions

Oseltamivir is generally well tolerated, gastrointestinal side effects (transient nausea, vomiting) may increase with increasing doses, particularly above 300 mg/day. Occasionally it may cause bronchitis, insomnia and vertigo. Less commonly angina, pseudo membranous colitis and peritonsillar abscess have also been reported. There have been rare reports of anaphylaxis and skin rashes. In children, most frequently reported side effect is vomiting. Infrequently, abdominal pain, epistaxis, bronchitis, otitis media, dermatitis and conjunctivitis have also been observed.

2. Supportive therapy

- IV Fluids.
- Parenteral nutrition.
- Oxygen therapy/ ventilatory support.
- Antibiotics for secondary infection.
- Vasopressors for shock.
- Paracetamol or ibuprofen is prescribed for fever, myalgia and headache. Patient is advised to drink plenty of fluids. Smokers should avoid smoking. For sore throat, short course of topical decongestants, saline nasal drops, throat lozenges and steam inhalation may be beneficial.
- Salicylate / aspirin is strictly contraindicated in any influenza patient due to its potential to cause Reye's syndrome.
- The suspected cases would be constantly monitored for clinical /radiological evidence of lower respiratory tract infection and for hypoxia (respiratory rate, oxygen saturation, level of consciousness).
- Patients with signs of tachypnea, dyspnea, respiratory distress and oxygen saturation less than 90 per cent should be supplemented with oxygen therapy. Types of oxygen devices depend on the severity of hypoxic conditions which can be started from oxygen cannula, simple mask, partial re-breathing mask (mask with reservoir bag) and non re-breathing mask. In children, oxygen hood or head boxes can be used.
- Patients with severe pneumonia and acute respiratory failure ($SpO_2 < 90\%$ and $PaO_2 < 60$ mmHg with oxygen therapy) must be supported with mechanical ventilation. Invasive mechanical ventilation is preferred choice. Non invasive ventilation is an option when mechanical ventilation is not available. To reduce spread of infectious aerosols, use of HEPA filters on expiratory ports of the ventilator circuit / high flow oxygen masks is recommended.
- Maintain airway, breathing and circulation (ABC);
- Maintain hydration, electrolyte balance and nutrition.
- If the laboratory reports are negative, the patient would be discharged after giving full course of oseltamivir. Even if the test results are negative, all cases with strong epidemiological criteria need to be followed up.
- Immunomodulating drugs has not been found to be beneficial in treatment of ARDS or sepsis associated multi organ failure. High dose corticosteroids in particular have no evidence of benefit and there is potential for harm. Low dose corticosteroids (Hydrocortisone 200-400 mg/ day) may be useful in persisting septic shock ($SBP < 90$).
- Suspected case not having pneumonia do not require antibiotic therapy. Antibacterial agents should be administered, if required, as per locally accepted clinical practice guidelines. Patient on mechanical ventilation should be administered antibiotic prophylactically to prevent hospital associated infections.

3. Discharge Policy

- Adult patients should be discharged 7 days after symptoms have subsided.
- Children should be discharged 14 days after symptoms have subsided.
- The family of patients discharged earlier should be educated on personal hygiene and infection control measures at home; children should not attend school during this period.

4. Chemo Prophylaxis

- All close contacts of suspected, probable and confirmed cases. Close contacts include household /social contacts, family members, workplace or school contacts, fellow travelers etc.
- All health care personnel coming in contact with suspected, probable or confirmed cases
- Oseltamivir is the drug of choice.
- Prophylaxis should be provided till 10 days after last exposure (maximum period of 6 weeks)
- By Weight:
 - For weight < 15 kg 30 mg OD
 - 15-23kg 45 mg OD
 - 24-40kg 60 mg OD
 - > 40 kg 75 mg OD
- For infants:
 - < 3 months not recommended unless situation judged critical due to limited data on use in this age group
 - 3-5 months 20 mg OD
 - 6-11 months 25 mg OD

5. Non-Pharmaceutical Interventions (Lindstrom SE,2004)

Close Contacts of suspected, probable and confirmed cases should be advised to remain at home (voluntary home quarantine) for at least 7 days after the last contact with the case. Monitoring of fever should be done for at least 7 days. Prompt testing and hospitalization must be done when symptoms are reported. All suspected cases, clusters of ILI/SARI cases need to be notified to the State Health Authorities and the Ministry of Health & Family Welfare, Govt. of India (Director, EMR and NICD). If a person becomes sick with swine flu, antiviral drugs can make the illness milder and make the patient feel better faster. They may also prevent serious flu complications. For treatment, antiviral drugs work best if started soon after getting sick (within 2 days of symptoms). Beside antivirals, supportive care at home or in hospital, focuses on controlling fevers, relieving pain and maintaining fluid balance, as well as identifying and treating any secondary infections or other medical problems. The U.S. Centers for Disease Control and Prevention recommends the use of Tamiflu (oseltamivir) or Relenza (zanamivir) for the treatment and/or prevention of infection with swine influenza viruses;

however, the majority of people infected with the virus make a full recovery without requiring medical attention or antiviral drugs.

The virus isolates in the 2009 outbreak have been found resistant to amantadine and rimantadine. In the U.S., on April 27, 2009, the FDA issued Emergency Use Authorizations to make available Relenza and Tamiflu antiviral drugs to treat the swine influenza virus in cases for which they are currently unapproved. The agency issued these EUAs to allow treatment of patients younger than the current approval allows and to allow the widespread distribution of the drugs, including by non-licensed volunteers. The best treatment for influenza infections in humans is prevention by vaccination. Work by several laboratories has recently produced vaccines.

The first vaccine released in early October 2009 was a nasal spray vaccine. It is approved for use in healthy individuals ages 2 through 49. This vaccine consists of a live attenuated H1N1 virus and should not be used in anyone who is pregnant or immunocompromised. The injectable vaccine, made from killed H1N1, became available in the second week of October. This vaccine is approved for use in ages 6 months to the elderly, including pregnant females. Both of these vaccines have been approved by the CDC only after they had conducted clinical trials to prove that the vaccines were safe and effective. However, caregivers should be aware of the vaccine guidelines that come with the vaccines, as occasionally, the guidelines change.

Future Aspects (Gramer MR, 2007)

Computer-assisted vaccine design

A new parameter has been defined to quantify the antigenic distance between two H3N2 influenza strains. This parameter was used to measure antigenic distance between circulating H3N2 strains and the closest vaccine component of the influenza vaccine. For the data between 1971 and 2004, the measure of antigenic distance correlated better with efficacy in humans of the H3N2 influenza A annual vaccine than did current measures of antigenic distance such as phylogenetic sequence analysis or ferret antisera inhibition assays.

This measure of antigenic distance could be used to guide the design of the annual flu vaccine. The antigenic distance combined with a multiple-strain avian influenza transmission model was used to study the threat of simultaneous introduction of multiple avian influenza strains. Population at Risk (PaR) can be used to quantify the risk of a flu pandemic and to calculate the improvement that a multiple vaccine offers.

CONCLUSION

The clusters of milder infections in the US suggest the virus is spreading readily among people. The US Centers for Disease Control and Prevention (CDC) says this strain is so different from existing human flu viruses that most people have no immunity to it.

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