SWINE FLU: INTRODUCTION AND ITS POSSIBLE REMEDIES

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Summary

Swine origin influenza was first recognized in the border area of Mexico and United States in April 2009 and during a short span of two month become the first pandemic. It is a subtype of influenza A i.e. H1N1 strain, which has undergone triple reassortment and contain genes from the avian, swine and human. Influenza virus is a member of the genus orthomyxovirus, family orthomyxoviridae. Influenza virus expresses two envelope glycoproteins: Hemagglutinin (H) and Neuraminidase (NA). Hemagglutinin is known to mediate of virus to the target cells via sialic acid residue in glycoconjugates.which plays a key role in viral infection. Neuraminidase is a critical protein of influenza virus.it helps the virus to spread around the body. Antiviral neuraminidase inhibitor attacks the influenza virus and prevents it from spread inside the body such as Oseltamivir and Zanamivir. Admantanes are resistant due to S31N mutation toward to inhibit the flu. The rise in oseltamivir-resistant influenza A (H1N1) viruses appears to be due to the spontaneous emergence and transmission of viruses with the H274Y mutation rather than selection as a result of increased oseltamivir use. There are two different brands of vaccines pandemrix and celvapan are now available. Herbal drugs such as tulsi, eldberry, ginger, garlic, lemon balm etc. can also be used in cure of infection. A number of sensitive and specific RT-PCR and real time PCR methods for detecting S-OIV and differentiating from seasonal H1N1. The incubation period range from 1 to 7 days and most likely from 1 to 4 days. Certain people are at high risk such as young children, people with various disorders such as CVS, neurological and liver disorder, asthma, immune suppression. Resident of nursing home or other chronic care facility.

Keywords: Swine flu (H1N1), Symptoms, Herbal approach

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Introduction

Currently, three main subtypes of influenza viruses are circulating in swine population throughout the world H1N1, H3N2 and H1N2 [1, 2]. Pigs can be infected by both bird (avian) influenza and the form of influenza that infect human. Pigs act as influenza mixing bowl at a place such as farm where the chickens, pigs and humans live in a close proximity. If the pig is infected with avian and human flu simultaneously the two types of virus may exchange genes. Such "reassorted" flu virus can sometime spread from pigs to people, which has happened this time in 2009 flu outbreak and the virus is freely passing between humans resulting in pandemic(3). Influenza virus expresses two envelope glycoproteins:

- Hemagglutnin(H)
- Neuraminidase(N)

An initial study reported that hospitalization was needed in almost 10% of cases, and the mortality rate was about 0.4% in case swine origin influenza virus infection (21&22).
The worldwide oseltamivir-resistant influenza A (H1N1) virus due to spontaneous emergence and transmission with H274Y frequency was low i.e. 0.33 %(17).

Structure of the virus was shown in figure-1

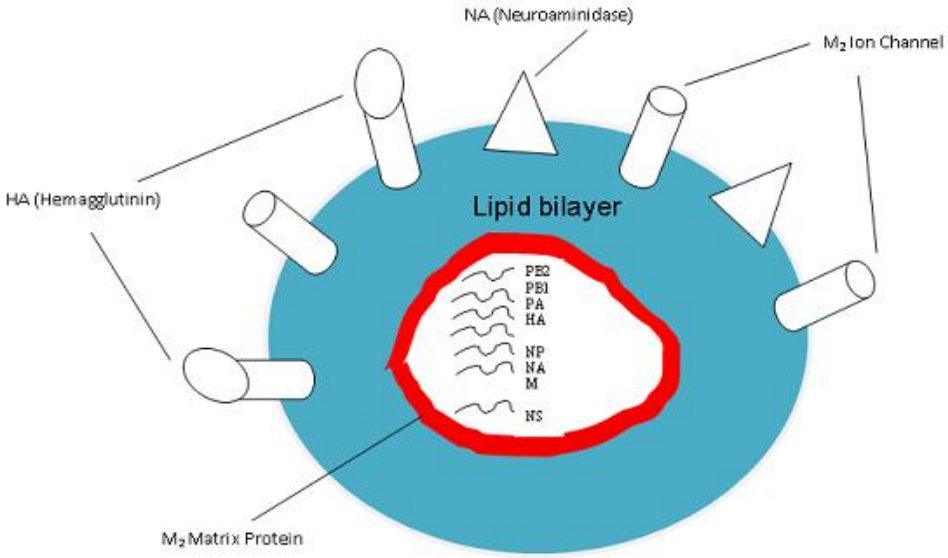

Figure-1

History

The term influenza derived from Italian word influence was coined in 1357 A.D as the disease was thought to be caused by influence of stars [4, 5]. In 1900, in North America, England and wales a major pandemic was reported [6]. In 1918-19: the worst pandemic so called Spanish flu affected nearly one third of the world population and caused 50 million-100 million death worldwide. This is also known as la pesadilla, a viral infectious disease caused by H1N1 type of influenza virus [7, 13]. It cause a cytokine storm in the body i.e. infected cells lead to the over stimulation of the immune system hence cytokines release in lung tissue. Which will further

leads to the extensive leukocytes migration towards the lung, causing destruction of lung cell and secretion of liquid into the organ. This makes the patient difficult to breathe [8-9]. It is indicated by the researchers that the 1918 virus descendent enzotically still persist in pigs and transmitted to humans and causing epidemics [9-11]. In 1957-58: in china originated avian influenza caused worldwide death estimated between 1-4 millions. In 1968: Millions death estimated to be caused by the Hong Kong flu [5].In 1976: the same strain caused a swine flu outbreak at fort Dix, United States among military recruits. It lasted for a month and then went away mystically. 240 people were infected [12]. In 1977-78: a pandemic Russian flu spread across Siberia and European arts of Russia. Flu epidemic caused by strain influenza A (H1N1) [13]. In1988: in September 1988, same strain caused a death of pregnant women due to pneumonia and infected people in Wisconsin, U.S.A [13]. In 1997: Avian flu outbreaks originated from new territories region in Northern Hong Kong.1.5 million Birds were slaughtered to minimize the spread of avian flu. In august 2002: influenza epidemic in Madagascar strain involved in the epidemic was type A influenza. In 2007: Department of agriculture officers investigated the outbreak of swine flu in Nueva Ecija and Central Luzon, Philippines and observed mortality due to hog cholera. All pigs in manila and five region of Luzon were slaughtered [18]. March, 2009: become apparent to public health officials in Mexico City. On 17 April, 2009: two cases in children were reported in California near the border of Mexico.29 April, 2009: Nine countries officials reported with the confirmed cases of swine influenza, of these Mexico, US, Austria, Canada, Germany, Israel, New Zealand, Spain and U.K reported the confirmed cases and death due to acute respiratory disease syndrome [19-20].

Antigenic Shift and Drift (14, 15)

The genetic changes that enable flu strain to jump from one animal species to another, including humans, are called antigenic shift or drift. As influenza virus is one of the most changeable of viruses.

Antigenic drift: The process of small and continuous genetic changes happens in influenza type A and type B as the virus make copies of itself is known as the antigenic drift. It is frequent enough to make the new strain of virus often unrecognizable to the human immune system.

Antigenic shift: The large and abrupt genetic changes happen in an influenza type A is known as the antigenic shift. It occurs when two different flu strains infect the same cell and exchange genetic material.

The novel assortment of HA or NA proteins in a shifted virus creates a new influenza A subtype as the people have the little or no immunity to such a new subtype ,therefore their appearance tends to coincide with a very severe flu pandemic or epidemic.

Fig2: Showing the triple reassortment between the pig, avian and human virus lead to origin of S-OIV due to Antigenic shift in pigs.

Flu viruses containing the genetic material from:

Pig Human Avian New strain

Figure-2- Antigen shift in pig

Mechanism of Action

Hemagglutnin is known to mediate the binding of virus to target cells via sialic acid residue in glyco-conjugate. This binding is the key step of viral infection [24].The NA facilitates the movement of the virus to and from the sites of the infection in the respiratory tract by taking charge of catalyzing the cleavage of neuraminic acid residue [24-26].Therefore the inhibition of influenza virus neuraminidase has the possibility of blocking an influenza virus infection [27].Hemagglutnin of influenza A viruses differ in specificity of binding from different species. Hemagglutin of human influenza A viruses generally recognize Sialyl α2-6 Gal-terminated saccharides. Whereas the hemagglutinin of avian influenza viruses recognize Sialylα2-3 Gal terminated saccharides [28-29].H1N1 virus strain binds to both α2-6 and α2-3 terminated sialic residues but weakly bind to the latter [30]. Human may be affected by both human and avian viruses as a human airway epithelial cell show 2, 3 and linked sialic receptors [31]. Avian and human viruses reassort in pigs and establish long term lineages in pigs; there is an ample of evidence for this. Reassortment between avian and human viruses implies of both viruses in the same host and same cell. Avian viruses are poorly permissive to human [32] and vice versa. Swine have been proposed as "mixing vessel" for the generation of pandemic viruses through Reassortment as they are permissive to both avian and human influenza viruses [33]. The change in glycolysation begin at day 3 after infection and still detectable at day 10. It is believed as a consequence of an influenza attack the mucinous cells in the ferret airways may become metaplastic and change their expression of sialoglycans [16, 33].

Symptoms [34]

- Fever
- Cough
- Sore throat
- Mild respiratory illness like nasal congestion and rhinorrhea.
- Vomiting and nausea
- Diarrhea
- Myalgia
- Fatigue/Arthralgia
- Headache
- Pneumonia
- Dyspnea
- Respiratory failure
- G.I upset

How Does It Spread?

Spread of swine influenza A (H1N1) virus is in the same way as the seasonal flu [35&36]. It is communicable i.e. swine flu spread mainly from person-to- person through coughing, sneezing of the infected person [37].

Incubation Period
It could range from 1 to7 days and most likely from 1 to 4 days [38]. This is comparable to the incubation period of avian influenza A (H5N1) that is 1-8 days [39] but longer than that of seasonal human influenza, which is 1 to 4 days [40].

Certain Groups at High Risk are [41]

1. Young children especially those are under 12 month of age.
2. Adults 65 years of age and older.
3. Persons with following conditions
    - Chronic pulmonary, cardiovascular, renal, hepatic, hematological, neurologic, neuromuscular, or metabolic disorders.
    - Immunosuppression, including that caused by medications or by HIV.
    - Pregnant women
    - Person younger than 19 years of age who are receiving long-term aspirin therapy.
    - Resident of nursing homes or other chronic care facilities

Infection Period
In general, persons with swine influenza virus infection should be considered potentially contagious as long as they are symptomatic and possibly for up to 7 days following illness onset or until symptoms resolve. Children, patients with lower respiratory tract infections, elderly and immunocomprised patients might be infectious for up to 10 days or longer [42-43]. This is due to low cytotoxic T-lymphocyte activity, which is responsible for viral clearance and recovery from infection [44].

Specimen Collection
To test for S-OIV, upper respiratory specimens, such as nasopharyngeal swab or aspirate, nasal wash, or tracheal aspirate should be collected with the appropriate personal protective precaution. For the patients who are intubated, an endotracheal aspirate should be collected. Bronchoalveolar lavage (BAL) sputum specimen is also acceptable. Specimen should be sent to the nearer laboratory, which has been equipped to test S-OIV. Ideally, swab specimen should be collected with a synthetic tip (e.g., Polyster or Dacron) and an aluminum or plastic shaft. Swabs with cotton tips and wooden shafts are not recommended. Specimens collected with swabs made of calcium alginate are not acceptable. The collection vial in which the swab is placed should contain 1-3ml of viral transport medium (e.g., containing, Protein stabilizer, antibiotics to discourage bacterial and fungal (4 ^{0}C) or refrigerated immediately for transportation to the laboratory. Once the sample arrived in the laboratory, they should be stored either in a refrigerator at 4 ^{0}C or in a -70 ^{0}C freezer. If a -70 ^{0}C freezer is not available, they should be kept refrigerated for no longer than 4 days. Specimen should be shipped on dry ice to the state public health laboratory [38, 45].
DIAGNOSIS:
World Health Organization recommends that suspected clinical cases of swine influenza infection are confirmed by :(46)

- Rapid influenza diagnostic tests (RIDT)
    - Antigen detection test(EIA)
    - Neuraminidase detection assay

- Direct and indirect immunofluorescence assays (DFA and IFA)
- Viral isolation in tissue cell culture
- Nucleic acid amplification tests (including rRT-PCR)
- Other serologic tests:

    - Hemagglutinin inhibition,
    - ELISA,
    - Complement –fixation
    - Neutralization.

A number of sensitive and specific RT-PCR and real time PCR methods for detecting S-OIV and differentiating from seasonal H1N1 (47 &48).
RT-PCR (conventional gel based PCR, real time RT-PCR, and multiplex PCR) test have a very high sensivity and specificity in comparison to other tests that is why highly recommended. Performance of these assays depends on patient's age, duration of illness, sample type, and viral type.

Drug Therapy

The SOIV is susceptible to Oseltamivir and Zanamivir, Neuraminidase inhibitor Antiviral medication. Which target the early phase of infection? However, this strain is resistant to admantanes such as Amantadine and Rimantadine (45).As neuraminidase is a critical protein of influenza virus. It helps the virus to spread around the body. Antiviral neuraminidase inhibitor attacks the influenza virus and prevents it from spread inside the body (27).

1. Oseltamvir

Oseltamivir is a prodrug of a potent and selective inhibitor of influenza virus neuraminidase enzymes. Oseltamivir is extensively converted to the active metabolite by esterase located predominately in the liver. The active metabolite, oseltamivircarboxylate, with an elimination half-life of about 6-10 h. active metabolite of oseltamivir inhibits neuraminidases of influenza viruses of both types A and B. It serves as the competitive inhibitor of sialic acid, found on the surface proteins of the normal host cells. By blocking the activity of the neuraminidase, oseltamivir prevents new viral particles from being released by infected cells (49).Adverse effects of oseltamivir include nausea, vomiting and transient neuropsychiatric events (self-injury or delirium). These dangerous side effects occur more commonly in children and adolescents. Nausea and Vomiting might be less severe if oseltamivir is taken with food (50).oseltamivir-resistant influenza A (H1N1) viruses rise due to the spontaneous emergence and transmission of viruses with the H274Y mutation rather than an increased oseltamivir use (51).

2. Zanamivir

Zanamivir is administered by inhalation with a dry powder inhaler. The bioavailability of the drug is 10-20% by inhalation, compared with 2% by the oral administration. About 90% of the absorbed dose is excreted unchanged in urine .The elimination half-life in serum of Zanamivir is about 2-5 h. The mechanism of action is similar to oseltamivir. Because Zanamivir therapy requires the patient to voluntarily inhale through the device, oseltamivir may be preferred over Zanamivir for young children. Zanamivir is not recommended for patients with chronic airway disease or asthma as it can induce bronchospasm (52).

Oseltamivir and Zanamivir are pregnancy category C drugs reflecting that clinical studies have not been done to assess the safety of their use during pregnancy (38,45).oseltamivir are preferred over Zanamivir during pregnancy. Both oseltamivir and Zanamivir are considered to be compatible with breastfeeding (53).
In addition to antiviral therapy, use of acetaminophen is important when fever is present, since hyperthermia during the first trimester has been associated with neural tube defects and other birth defects.in addition; fever during labor is a risk factor for neonatal seizures, encephalopathy, cerebral palsy and neonatal death (54). Children who may have influenza infection should not take aspirin or aspirin-containing products, such as bismuth subsalicylate due to the increased risk of Reye's syndrome (55).

Add n Therapy
Such as antibiotics should be used at the discretion of the clinicians if the patient's clinical condition warrants. Patient with pandemic S-OIV infection should be treated empirically for community acquired pneumonia (56).
Role of corticosteroids in the management of severely ill patients with novel S-OIV infection unclear and routine corticosteroid use is not recommended. Patients in septic shock require vasopressor and have suspected adrenal insufficiency recommended low dose of corticosteroids (57).

Herbal Approach

1. Elderberry
Elderberry (Sambucus nigra), an herb with anti-viral, is increasingly considered as a natural – defense against the H1N1 swine flu. The binding blocked the ability of the viruses to enter host cells and thereby effectively preventing H1N1 infection in vitro.it contains flavonoids are powerful natural antioxidants that work to protect the body's cells from the potential damaged caused by the free radical. Certain flavonoids –anthocyanin are found preliminary in the pigment of dark blue and deep purple fruits such as the black berry. One such popular preparation of elderberry is SAMBUCOL, the syrup available (77, 78).

2. **Japanese Wasabi Leaves**
Japanese Wasabi (Wasabia japonica) is now habitually used as a spice in some kinds of Japanese foods and its pungent taste and flavor are preferred. The leaf area of summer leaf is far greater than that of winter leaf but the anti-influenza virus activity is the same. The ethanol extract inhibited influenza virus replication regardless of the hemagglutinin antigen type (79).

3. Red Fleshed Potatoes
Bred red fleshed potatoes are hybrid seedlings between cultivars of Solanum tuberosum ssp. Tuberosum and S.tuberosum ssp.andigena. The anthocyanin of red fleshed potato inactivated both influenza viruses A (IVA) and B (IVB). The IC50 of the red fleshed potato anthocyanin was 48 μg/ml (for IVA) and 54μg/ml (for IVB) [80].

4. Tulsi
Ocimum sanctum several formulation enhances immunity and metabolic functions as well as in the management of respiratory problems. Chemical constituents- a variety of biological compounds have been isolated from the leaves including ursolic acid, apigenin and luteolin. Recent pharmacological studies have established that anabolic, hypoglycemic, smooth muscle

relaxant, cardiac depressant, adaptogenic and immunomodulator properties of this plant. Essential oil of tulsi has antibacterial, antifungal and antiviral properties (81).

5. Licorice

The root of Glcyrrhiza glabra is a powerful antiviral. The licorice root contain numerous compounds, including glycyrrhizic acid (GA).This acid inhibit the replication of several viruses in vitro.it administered intravenously in therapeutic situations because when taken orally, GA is mostly hydrolyzed to glycyrrhetic acid by bacteria in gastrointestinal tract before GA can be absorbed. Licorice is used for treating symptoms of flu such as sore throat, bronchitis, and coughs and is known to boost adrenal function (80, 83).

6. Lemon Balm

It is a powerful antiviral that the active ingredient has been isolated by scientist and it is currently sold in Germany as "Lomaherpan" to cure herpes. Lemon balm also relives many of the symptoms of flu such as reliving cramps and gas, stopping spasms and relieving pain. Use fresh or freeze –dried leaves in a tea (82).

7. Garlic

Garlic is antiviral and antibacterial, and several of the sulfur compounds in garlic are active against the flu virus. For the most potent result it is suggested to have around 4 cloves a day as a preventive measure, and around 16 cloves a day if once get flu (84).

8. Juniper

Juniper contains a potent antiviral compound i.e. deoxy podophyllotoxin that seems to inhibit many different viruses (85).

9. Shiitake

This mushroom has antiviral and immune stimulating properties.it contains a compound called Lentinan that has been found to protect against viral encephalitis in mice (80).

Resistance to Admantanes

The M2 channel is considered to play in a viral life cycle(58, 63).the M2 channel of influenza virus is a homo tetrameric protein contain trans membrane four helix channel with 97 residue per subunit ,comprises an intracellular C terminal domain with length of 19 residue and an extracellular N-terminal domain of 24 residue(58-61). The protein has a major function as aproton selective channel which is regulated by endosomal pH values (62-64).

The uncoating process of the viral nucleic acid in endosomes will be activated i.e. essential for virion to invade the host cells, as proton flux into virion (64-65). Additionally this channel (M2) has another function to preserve the pre fusion state of HA during viral maturation (66-68). Admantanes are not predicted to be able to inhibit the M2 function and have completely lost their binding with the M2 residue. This is due to the fact that the M2 transmembrane of the novel H1N1 strain contain S31N mutation which is known to confer the resistance to admantanes (69). The changing from M2 channel of avian influenza H5N1 to a novel H1N1 influenza, three residues V28, S31and L43 were replaced by I28, N31 and T43.Amongest these S31N is the common mutations which confer the resistance (70).

Vaccination

There are two different brands of vaccines pandemrix and celvapan. Many people with pandemrix vaccine will only need one dose. People with celvapan will need two doses three weeks apart. The seasonal flu vaccine does not protect against swine flu.

People at high risk will get the vaccine first.

Who cannot have the swine flu vaccine:

- Who has had a severe allergic reaction to a previous dose of the vaccine or any component of vaccine?
- People with egg allergies as pandemrix vaccine are prepared in the hen's egg in same way as the seasonal vaccines.

Side effects of vaccines:

- Redness, soreness and swelling at site of injection.
- Fever
- Headache
- Muscle ache

Both the vaccines are licensed vaccines (71).

Pandemrix, made by GlaxoSmith Kline (GSK), Focetria, made by Novartis and Celvapan made by Baxter were approved by the European Medicines agency (72-75).A robust immune response was produced in over 90% of patients after a single dose of either 15 or 30 μg of antigen.

Arepanrix, as AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine similar to Pandemrix and also made by GSK, was authorized by Canada's Minister of Health on 21 October 2009(76).

Conclusion

Swine origin influenza virus is communicable disease i.e. transmit through person -to-person. The oseltamivir (Tamiflu) and Zanamivir (Relenza) is prescribed. Now a day's vaccine such as pandemrix and celvapan is also available as prophylaxis. Oseltamivir is preferred over Zanamivir during pregnancy. Both oseltamivir and Zanamivir are considered to be compatible with breastfeeding. Children who may have influenza infection should not take aspirin or aspirin-containing products, such as bismuth subsalicylate due to the increased risk of Reyes syndrome. Celvapan vaccine is not prepared by using eggs. So, this vaccine can be taken by who have allergy to egg as in this case pandemrix can't be given as it prepared by using egg.

Avoid close contact i.e. is being within 6 feet with people who have flu like symptoms.

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