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Influenza and its management: an overviewM. M. Gupta^{1*}, Vandana Kumari² and Pankaj Arora¹

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Abstract

Influenza is an acute infectious disease probably due to a filterable virus, characterized by fever, catarrhal inflammation of the respiratory or gastro- enteric tract, or profound nervous disturbances marked by headache, insomnia, convulsions, delirium, neuritis or mental depression. The influenza virus is notoriously known for its unique ability to cause recurrent epidemics and global pandemics during which acute febrile respiratory illness occurs explosively in all age groups. The present paper highlights all these aspects of influenza and its management.

Key- Words: Influenza, Management, Disease, Virus

Introduction

Influenza is an acute infectious disease probably due to a filterable virus, characterized by fever, catarrhal inflammation of the respiratory or gastro- enteric tract, or profound nervous disturbances marked by headache, insomnia, convulsions, delirium, neuritis or mental depression. The epidemiological spread of the influenza virus is due to 1) its ability to emerge and circulate in avian or porcine reservoirs by either genetic re-assortment or direct transmission and subsequently spread to humans at irregular intervals, 2) its ability to produce fast and unpredictable antigenic change of important immune target, after its establishment in a human body.

The pathogenicity and virulence of the influenza virus can be determined by host factors and viral factors. The host factors includes presence of target receptors in host cells, availability of enzymes in host cells which are essential for viral entry and replication, state of immunocompetence of the individual host, specific immunity against certain viral epitopes in the individual host and target population, ability of the immune system to control the viral replication

effectively without causing serious collateral damage for the host by its inflammatory response whereas the viral factors includes ability to bind to the host cells and ability of virus shedding, restriction of cytopathogenic effects to allow for an appropriate balance between viral replication and control by the host, escape from immunosurveillance by evolution of antigenic variation driven by selective pressure of the immune response, escape from immunosurveillance by recombination with different virus strains from zoonotic disease, modulation of the immune response to attenuate effective host defense mechanisms.

Structure of influenza virus

Influenza viruses are enveloped single-stranded RNA viruses with a pleomorphic appearance, and an average diameter of 120 nm. They are spherical or filamentous in structure and when sliced transversely, influenza virions resemble a symmetrical pepperoni pizza, with a circular slice of pepperoni in the middle and seven other slices evenly distributed around it. Human influenza viruses are members of the orthomyxovirus family, which consists of the genera: influenza A, B, and C virus, and Thogovirus (in ticks). In humans, only influenza A and B viruses are of epidemiological interest. The influenza A and B virus genomes consist of 8 separate segments covered by the nucleocapsid protein together these build the ribonucleoprotein (RNP), and each segment codes for a functionally important protein.

- Polymerase B2 protein (PB2)
- Polymerase B1 protein (PB1)

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- Polymerase A protein (PA)
- Haemagglutinin (HA or H)
- Nucleocapsid protein (NP)
- Neuraminidase (NA or N)
- Matrix protein (M): M1 constructs the matrix; and in influenza A viruses only, M2 acts as an ion channel pump to lower or maintain the pH of the endosome
- Non-structural protein (NS); the function of NS2 is hypothetical

The main antigenic determinants of influenza A and B viruses are the haemagglutinin (H or HA) and neuraminidase (N or NA) transmembrane glycoproteins. Based on the antigenicity of these glycoproteins, influenza A viruses are further subdivided into sixteen H (H1-H16) and nine N (N1-N9) subtypes.

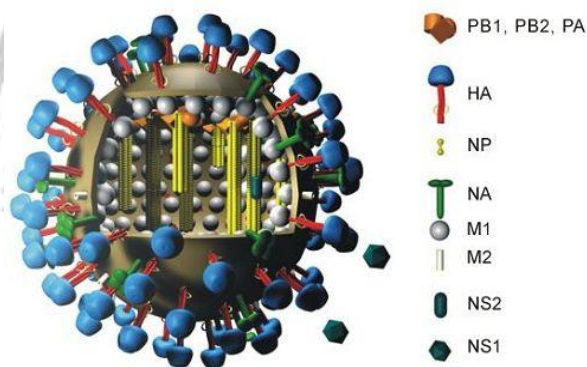


Fig.1: Structure of influenza A virus.

Individual management

This includes three prophylaxis defense lines which are prophylactic exposure, vaccination, prophylactic use of antiviral drugs or one treatment defense line antiviral drugs. Infected individuals may be infectious for as long as 24-48 hours before the onset of symptoms. Prophylactic exposure is virtually impossible during an ongoing epidemic or pandemic, especially in our highly mobile and densely populated world.

Prophylactic exposure is related to basic personal hygiene measures which include regular hand-washing among family members of patients. In general, people should be discouraged to touch their eyes nose or mouth. Minimize the impact of sneezes and coughs by all possible means.

Vaccination against the prevalent wild-type influenza virus is recommended for all individuals in high-risk groups, including those aged 65 years or older, and those with chronic illness, particularly diabetes, chronic respiratory and cardiac disease, and persons immune compromised from disease or concomitant therapy. In addition, it is generally recommended that all healthcare personnel be vaccinated annually against influenza.

In healthy primed adults, the efficacy after one dose may be as high as 80-100% whereas in unprimed adults (those receiving their first influenza immunization), efficacy is in this range after two doses. With some underlying conditions (i.e., HIV infection, malignancies, renal transplantation), efficacy is lower; however protection ultimately depends on who is vaccinated and on the match between the vaccine and the circulating virus. Inactivated vaccine reduces exacerbations in patients with chronic obstructive pulmonary disease. Influenza vaccines are efficacious in children older than two years but little evidence is available for children under two. Nasal spray of live vaccines seemed to be better at preventing influenza illness than inactivated vaccines.

In selected populations, antiviral drugs may be a useful option in those not covered or inadequately protected by vaccination. It should be emphasized though that the prophylactic use of available antiviral drugs is by no means a substitute for the yearly vaccination recommended by national health services.

Candidates for short-term prophylactic use of antiviral drugs are high-risk patients who are vaccinated only after an epidemic has already begun, as well as unvaccinated high-risk contacts of an individual with influenza. In some cases, prophylaxis could be indicated when a current epidemic is caused by a strain which is not represented in the vaccine. Of the two available drug classes, the adamantanes recently came under pressure when the global prevalence of adamantane-resistant influenza viruses was found to have significantly increased from 0.4% in 1994-1995 to 12.3% in 2003-2004. It is believed that the elevated incidence of resistance is due to increased use of over-the-counter amantadine after the emergence of severe acute respiratory syndrome (SARS).

On the basis of the resistance results it is recommended that neither amantadine nor rimantadine be used for the treatment or prophylaxis of influenza A, then oseltamivir or zanamivir should be selected for the treatment and prophylaxis.

Epidemic treatment

In uncomplicated cases, bed rest with adequate hydration is the treatment of choice for most adolescents and young adult patients. Antibiotic treatment should be reserved for the treatment of secondary bacterial pneumonia.

The older drugs, rimantadine and amantadine, are only effective against influenza A virus. If rimantadine and amantadine are used, it is important to reduce the emergence of antiviral drug-resistant viruses. Amantadine or rimantadine treatment should therefore be discontinued as soon as possible, typically after 3-5 days of treatment, or within 24-48 hours after the

disappearance of signs and symptoms. The newer neuraminidase inhibitors are licensed for treatment of patients aged 1 year and older (oseltamivir) or 7 years and older (zanamivir). They are indicated in patients with uncomplicated acute illness who have been symptomatic for no more than 2 days. The recommended duration of treatment for both drugs is 5 days.

Pandemic prophylaxis

The problem with a new pandemic influenza strain is that there is no hiding place on earth. Virtually any single human being will eventually become infected with the new virus. Antibodies will provide some protection against the new influenza strain, but to develop antibodies you have to either be infected or vaccinated.

Once a new virus has been shown to be effectively transmitted among humans, it will take approximately 6 months to start the production of the corresponding vaccine. Thereafter, vaccine supplies will be exquisitely inadequate, and years will be needed to produce enough vaccine for 6.5 billion people.

A commonly observed phenomenon in infectious diseases is that pathogens become less virulent as they evolve in a human population. This would favour the second option, i.e., of avoiding a new influenza virus for as long as possible. An additional advantage of this choice is that several months after the start of the pandemic, the initial chaos the health systems will inevitably face during a major outbreak, will have at least partially resolved.

The most extreme option of avoiding influenza would be to flee to remote areas of the globe - a mountain village in Corsica, the Libyan Desert, or American Samoa. That might work but it might not.

If the direct and unprotected confrontation with the new virus becomes inevitable, some protection is still possible: face masks and social distancing.

Pandemic treatment

We don't know whether the next pandemic influenza strain will be susceptible to the currently available antiviral drugs. If it is caused by a H5N1 virus, the neuraminidase inhibitors oseltamivir and zanamivir may be critical in the planning for a pandemic.

Experience in treating H5N1 disease in humans is limited and the clinical reports published to date include only a few patients. In particular, the optimal dose and duration of oseltamivir treatment is uncertain in H5N1 disease, and the following preliminary recommendations have been proposed. Start treatment with oseltamivir as soon as possible. As H5N1 infections continue to have a high mortality rate, consider treatment even as late as 8 days after onset of symptoms, if there is evidence of ongoing viral

replication. Consider increasing the dose of oseltamivir in severe disease (150 mg twice daily in adults) and continue treatment for longer periods (7-10 days or longer). Although oseltamivir is generally well tolerated, gastrointestinal side effects in particular may increase with higher doses, particularly above 300 mg/day.

Global management

The management of an influenza outbreak is well-defined for epidemics, and less well-defined for pandemics.

Epidemic management

As influenza viruses mutate constantly, vaccine formulations need to be re-examined annually. Vaccine production is a well-established procedure throughout the year, influenza surveillance centres in 82 countries around the world watch circulating strains of influenza and observe the trends. The WHO then determines the strains that are most likely to resemble the strains in circulation during the next year's winter seasons, and vaccine producers start vaccine production. The decision on the composition of the next "cocktail" is made each year in February for the following northern hemisphere winter and in September for the following southern hemisphere winter.

Predicting the evolutionary changes of the viral haemagglutinin is not easy and not always successful. In years when the anticipated strain does not match the real world strain, protection from influenza vaccine may be as low as 30%.

Pandemic management

Serious influenza pandemics are rare and unpredictable events. Managing unedited situations requires some appreciation of the magnitude of the problems that lie ahead. The impact on human health may be highly variable and is expressed in the number of infected individuals, clinically ill individuals, hospitalized patients, deaths.

The three defense lines are containment, drugs, and vaccines. Containment and elimination of an emergent pandemic influenza strain at the point of origin has been estimated to be possible by a combination of antiviral prophylaxis and social distance measures. To this purpose, the WHO has recently started creating an international stockpile of 3 million courses of antiviral drugs to be dispatched to the area of an emerging influenza pandemic.

Once a pandemic is under way and vaccines have not yet become available, national responses depend on the availability of antiviral drugs. As demand for the drug will exceed supply, stockpiling of antiviral drugs, either in the form of capsules or the bulk active pharmaceutical ingredient, has been considered a viable option by some governments.

Until now, mainly oseltamivir has been used to constitute stockpiles of neuraminidase inhibitors. After the recent isolation of oseltamivir-resistant isolates in serious H5N1 infection, other antiviral agent zanamivir to which oseltamivir-resistant influenza viruses remain susceptible should be included in treatment for influenza A (H5N1) virus infections.

In an ideal world, we would have 6.5 billion vaccine doses, the day after the pandemic starts; in addition, we would have 6.5 billion syringes to inject the vaccine; and finally, we would have an unlimited number of health personnel to administer the vaccine.

We don't live in an ideal world. At present, the world has a production capacity of about 300 million trivalent influenza vaccines per year, most of which is produced in nine countries. 300 million trivalent influenza doses translate into 900 million univalent doses, enough to vaccinate 450 million people with an initial vaccination and a booster dose if the H5N1 vaccine is sufficiently immunogenic. Mainly oseltamivir, rimantadine and zanamivir are used in the management of influenza

Oseltamivir

The Recommended oral dose of oseltamivir suspension for treatment of influenza in paediatric patients or adults.

Table No. 1: Recommended oral dose of oseltamivir suspension

Body Weight (Kg)	Recommended dose for 5 days
≤ 15 kg	30 mg twice daily
> 15 -23	45 mg twice daily
> 23 – 40	60 mg twice daily
> 40	75 mg twice daily

A 75 mg capsule may be a viable formulation in children (e.g. over 8 years of age) who are able to swallow solid dosage forms. For prophylaxis, the recommended dose of oseltamivir is 75mg once daily for at least 7 days.

The recommended oral dose of oseltamivir suspension for paediatric patients aged 1 year and older following contact with an infected individual is according the following table

Table No. 2: Recommended oral dose of oseltamivir suspension in case of infected individual by following contact

Body Weight (Kg)	Recommended dose for 7 days
≤ 15 kg	30 mg once daily
> 15 -23	45 mg once daily
> 23 – 40	60 mg once daily
> 40	75 mg once daily

Rimantadine

It is recommended for both prophylaxis and treatment of influenza A in adults and children. The recommended dose is 100 mg twice a daily but a dose reduction to 100 mg daily is recommended in patients with severe hepatic dysfunction, renal failure (CrCl ≤ 10 ml/min), elderly nursing home patients and patients with any degree of renal insufficiency. These cases should be closely monitored with dosage adjustments being made as necessary.

For treatment, rimantadine should be initiated within 48 hours after the onset of signs and symptoms of influenza A infection. Therapy should be continued for approximately seven days from the initial onset of symptoms.

For children rimantadine is licensed for prophylactic use only. Children less than 10 years of age should receive 5 mg/kg but not exceeding 150 mg. Children 10 years of age or older receive the adult dose.

Zanamivir

The recommended dose of zanamivir for the treatment of influenza in adults and paediatric patients aged 7 years and older is 10 mg twice a day (twice daily 2 consecutive inhalations of one 5-mg blister) for 5 days. On the first day of treatment, two doses should be taken at least 2 hours apart. On the following days, doses should be taken about 12 hours apart. No dosage adjustment is required in patients with renal impairment.

Conclusion

Epidemiological studies of the 20th century pandemics offer some insight into what can be expected when the next influenza pandemic occurs.

Pandemic influenza is not always like a sudden storm, followed by return to clear skies. Instead, mortality rates can remain elevated for several years during which time an effective vaccine would be in high demand.

In all three pandemics in the twentieth century, the majority of associated deaths occurred in 6 months to a year after the pandemic virus first emerged, suggesting that the intense and timely surveillance of both age-specific mortality and new influenza viruses could provide sufficient time for production and distribution of vaccines and antivirals to prevent much, if not most, of the mortality impact.

At present, H5N1 avian influenza remains largely a disease of birds. The species barrier is significant despite the infection of tens of millions of poultry over large geographical areas for more than two years, fewer than 200 human cases have been confirmed by a laboratory. Human cases, first documented in 1997, coincided with outbreaks of highly pathogenic H5N1 avian influenza in poultry. Very limited human-to-

human transmission of the H5N1 strain was documented in healthcare workers and family members with contact. Although H5 antibodies were detected in these groups, indicating infection with the virus, no cases of severe disease occurred.

Until now, the disease has predominantly affected children and young adults. The reason for this age distribution (exposure risk, disease reporting bias, intrinsic host issues, etc.) is unclear. Likewise, it is not known whether, and to what extent, genetic composition plays a role in the susceptibility and resistance to infection with H5N1 influenza virus.

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