UNIT NO. 2

INFLUENZA AND PATIENTS WITH CHRONIC DISEASES AND ELDERLY

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ABSTRACT

Influenza is a highly contagious viral illness characterized by fever, cough, headache and myalgia. The influenza virus is a segmented ribonucleic acid (RNA) virus that can infect both humans and animals, and the capacity for reassortment when multiple viruses infect the same cell has led – and will continue to lead – to the development of novel pandemic influenza A viruses. The disease is generally self-limiting, although complications and deaths can occur, particularly in children < two years of age, adults >65 years of age, pregnant women, and immunosuppressed individuals. Specific antiviral therapy is available, including oseltamivir in Singapore, and is recommended for severe disease as well as those with higher likelihood for developing complications from influenza. In addition to hand hygiene and respiratory etiquette, antiviral prophylaxis may reduce the impact and burden of influenza in household and institutional settings. However, the primary means for preventing influenza is via annual vaccination in those above the age of two years. The influenza vaccine, while having variable efficacy depending on antigenic matching with circulating viruses each year, is safe and cost-effective at the population level.

Influenza, oseltamivir, influenza vaccine, neuraminidase inhibitors, antigenic shift, antigenic drift

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INTRODUCTION

Influenza is a highly contagious illness caused by the eponymous influenza virus. There are three recognized serotypes of influenza that can infect humans[1]:

- Influenza A which infects both humans as well as other mammals and birds, and has multiple subtypes based on combinations of the two surface proteins hemagglutinin (H) and neuraminidase (N).
- Influenza B which infects humans and seals.
- Influenza C which infects humans and pigs, but only causes very mild disease.

It is a segmented RNA virus, which means that in addition to the accumulation of mutations that occur in the viral genome over the course of time (which results in antigenic drift), entire gene segments can be exchanged in a process termed reassortment when different influenza viruses co-infect the same cell, resulting in chimeric genomes and novel virus genotypes (which results in antigenic shift) [2]. The vast majority of mutations and reassortments results in non-viable or less fit viruses, but occasionally, increased fitness and/or virulence occurs[2].

Antigenic drift – where the accumulated mutations result in viruses that are not inhibited effectively by antibodies that target their predecessors – partially explains why humans and animals can repeatedly develop influenza[3]. It is also one of the reasons for the recommendation for annual influenza vaccination[3].

In antigenic shift, different human and animal influenza viruses may reassort into novel viruses, which has resulted in five influenza pandemics over the past century[4].

Clinical Aspects

Influenza is spread primarily by droplets, although contact and airborne transmission can also occur. The incubation period for influenza is approximately two days and the disease are generally self-limiting, with the risk of transmission being highest in the first four days of illness[1].

Patients typically present with sudden onset of fever accompanied by myalgia, headache, coughing and sore throat. Gastrointestinal symptoms such as loss of appetite, vomiting and diarrhea can occur, while lower respiratory tract infection including croup and pneumonia is less common. Rare complications include neurological involvement (encephalopathy, Guillain-Barré syndrome, transverse myelitis and acute necrotizing encephalitis have been described) myositis, and cardiac involvement (myocarditis) [1].

Although primarily a transient inconvenience for most, influenza poses a higher risk of mortality and complications in the very young, pregnant women, the very old, and the immunocompromised (Table 1)[1, 5-6]. During the 2009 H1N1 pandemic, pregnant women were found to be at a higher risk of influenza-associated complications and mortality, as well as adverse maternity outcomes[6]. At the population level, a surge of influenza cases, which can happen in seasonal epidemics or in pandemics, can overwhelm health systems and hospitals, impairing the ability to provide routine healthcare to the public and potentially even affecting health outcomes unrelated to influenza negatively[7, 8].

A recent statistical modelling approach estimated the global excess influenza-associated respiratory mortality rate at 4.0 –

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8.8 per 100,000 persons annually, affecting those above 75 years of age disproportionately (17.9 – 223.5 per 100,000 persons vs. 0.1 – 6.4 per 100,000 persons for people younger than 65 years)[5]. Although Singapore data were not used in this study, it is plausible that our excess influenza-associated respiratory mortality rate should be similar to that of the other developed countries, which was 3.9 – 6.4 per 100,000 persons per year (translating to approximately 22 to 36 deaths a year)[5].

Treatment of influenza

Other than supportive therapy, a handful of antiviral drugs have received United States Food & Drug Administration's (FDA) approval for the treatment of influenza. There are three neuraminidase inhibitors (oseltamivir, zanamivir, peramivir – the first two are available in Singapore), while the latest is an endonuclease inhibitor (baloxavir marboxil – not available in Singapore). In healthy adults and children, these drugs reduce the duration of symptoms by a day on average[9-12]. However, their effect on immunocompromised and other vulnerable populations is less clear, with limited evidence available from clinical studies and randomized control trials[9-12, 14].

One event worth recounting is the successful four-year (2009-2013) public campaign by the British Medical Journal and Cochrane researchers to compel Roche to make available previously unpublished clinical study data and reports on oseltamivir[14]. This arose as a consequence of a lack of transparency as well as resistance against releasing the data obtained by Roche (the makers of oseltamivir) during clinical trials and studies that the pharmaceutical company had commissioned. The outcome was a re-analysis which concluded that oseltamivir did not prevent the development of complications in healthy adults and children with influenza[9]. The importance of this campaign cannot be understated even within the limited scope of oseltamivir and influenza, as government had spent (and continue to spend) billions in stockpiling oseltamivir for influenza pandemics, at the recommendation of the World Health Organization (WHO) [13]. In 2017, WHO downgraded the status of oseltamivir from a "core drug" to a "complementary drug"[13]. However, the United States Centers for Disease Prevention and Control's (US CDC's) position on oseltamivir did not change – they had conducted their own clinical trial in Bangladesh[10] and a subsequent meta-analysis that included this trial appeared to demonstrate the reduction in respiratory complications in influenza patients treated with oseltamivir[11].

How then should one decide on who should be prescribed antiviral drugs for treatment of influenza during seasonal epidemics? The US CDC and European Centre for Disease Prevention and Control (ECDC) recommendations are similar in this regard, despite the paucity of clinical evidence in vulnerable populations[13, 15]:

- Healthy and symptomatic adults and children with confirmed or suspected influenza, who are not at high risk of complications from influenza – antiviral treatment can be initiated on an individual basis (US CDC adds a further clause of illness onset being <48 hours).
- Population subsets deemed at higher risk of complications (Table 1) with confirmed or suspected influenza – antiviral treatment is recommended as early as possible.
- Hospitalized patients with any age with confirmed or suspected influenza – antiviral treatment is recommended as early as possible (ECDC also includes in this group residents of long-term care facilities).
- US CDC also recommends antiviral medications for non-hospitalized patients with "severe, complicated or progressive illness"[15].

The antiviral drugs listed above are generally safe, with the neuraminidase inhibitors such as oseltamivir eliciting a small concomitant increase in the risk of gastrointestinal side effects such as nausea and vomiting during the clinical trials for influenza treatment[9-11], whereas psychiatric adverse effects were seen during the prophylaxis trials[9, 10].

Prevention of influenza

At the population level, annual influenza vaccination remains the most cost-effective intervention to reduce the burden of influenza[13, 15]. There are other complementary strategies, the most important of which are infection control measures including hand hygiene and respiratory etiquette[1, 15, 16]. Oseltamivir has also been used in a variety of settings as either pre- or post-exposure prophylaxis, including households, long-term care facilities, and in the military[8, 9, 11, 13, 15-17]. In the only Singapore published experience, Lee and co-workers showed during the 2009 H1N1 pandemic that the use of oseltamivir as ring prophylaxis in military camps, along with rapid identification and isolation of infected personnel, effectively reduced the impact of the pandemic in these camps[17].

There are currently three different types of influenza vaccine available – inactivated, live attenuated and recombinant – all of which have significant limitations, the two most important being:

- Vaccine seed viruses must be replaced at intervals to match the antigenic drift of the circulating influenza viruses[1, 18].
- Intra-seasonal waning of immunity post-vaccination has been widely reported, particularly for the H3N2 component of the vaccine[19, 20]. This means that even within a short period of several months, the immunity conferred by the vaccine can be lost.

Unfortunately, there is no universal vaccine for influenza at present. In Singapore, trivalent (usually H1N1, H3N2 and B virus) and quadrivalent (two influenza B viruses) inactivated influenza vaccines are widely available, although the former will eventually be phased out.

WHO organizes biannual influenza vaccine composition meetings for northern and southern hemispheres (Singapore is classified by WHO as being in the "northern hemisphere" for the purposes of influenza vaccination) in order to attempt to predict the correct seed viruses based on the genetic and

antigenic characteristics of circulating viruses detected by the WHO Global Influenza Surveillance and Response System[18,19]. The recommendations of these advisory panel of experts are then used by pharmaceutical companies to develop and produce the influenza vaccines for the northern and southern hemispheres[19]. A mismatch would result in a less effective vaccine for that hemisphere that year.

US CDC has studied and published the results of the seasonal influenza vaccine's efficacy every year since 2004, and this figure has varied between ten percent and 60 percent, with the recent average being around 40 percent[21]. Despite these low figures, however, the vaccine's utility is clear. In three separate meta-analyses that have been deemed "stabilized" (i.e. the weight of evidence is such that results are unlikely to change with the inclusion of new studies[22]), Cochrane reviewers estimated:

- In the elderly (>65 years old), 30 and 42 individuals on average would need to be vaccinated in order to prevent a case of influenza and influenza-like-illness (ILI) respectively[23]. The evidence relating complications from vaccination was of poor quality and provided little guide to public health policy[23].
- In healthy adults including pregnant women, 71 and 29 individuals on average would need to be vaccinated in order to prevent a case of influenza and ILI respectively [24]. The protective effect in pregnant women and newborns was likely to be modest. There was no association between vaccination and severe adverse events in the studies reviewed[24].
- In healthy children between age three and 16 years, just five and 12 children on average would need to be vaccinated with inactivated influenza vaccines to prevent a case of influenza and ILI respectively. The impact on serious complications of influenza or school absenteeism was uncertain[25].

Current influenza vaccines are very safe, with the most common adverse effects being injection site pain and erythema, as well as low grade fever[23-25]. Although an egg-based manufacturing process is used for both inactivated and live influenza vaccines, only trace amounts of egg protein is present in them, and the vaccines are safe even for those with severe egg allergy. A practice update published in 2017 by the Joint Task Force on Practice Parameters in the US – comprising members from American Academy of Allergy, Asthma, and Immunology as well as the American College of Allergy, Asthma, and Immunology – have concluded that egg allergy is not a contraindication for the current influenza vaccines[26].

While the number needed to vaccinate in order to prevent a case of influenza and ILI seems high, particularly in healthy adults, the relatively low cost and safety of influenza vaccines has resulted in this intervention being determined to be cost-effective in numerous studies and country settings[13, 15, 27].

CONCLUSIONS

Influenza is a viral illness with a significant global disease burden and pandemic potential. Although virtually always self-limiting in healthy individuals, complications and deaths may occur, particularly among immunosuppressed population groups. Treatment is largely supportive, although targeted antiviral drugs exist which may reduce the duration of symptoms. Despite the fact that these drugs are internationally recommended for the treatment of those who are immunosuppressed and/or with severe influenza, actual evidence of clinical efficacy remains weak at present. Vaccines against influenza currently provide only short-term protection at best, and annual vaccinations are recommended. They are however cost-effective at the population level in preventing influenza.

Conflicts of Interest

Nil declared.

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Table 1: Population subsets deemed at higher risk for developing complications following influenza infection[1, 15]

Population subset	Examples of subsets
Extremes of age	• <two years of age • >65 years of age
Chronic respiratory disease	• Asthma requiring repeated use of inhaled or systemic steroids. • Chronic obstructive pulmonary disease • Other chronic lung diseases, i.e. bronchiectasis, interstitial lung disease, etc. • Children previously hospitalized with lower respiratory tract disease.
Chronic heart disease	• Congenital heart disease • Chronic heart failure • Hypertension with cardiac complications • Ischemic heart disease on regular clinical follow-up
Chronic renal disease	• Chronic renal failure including those on dialysis • Renal transplantation • Nephrotic syndrome
Chronic liver disease	• Cirrhosis • Chronic hepatitis • Liver transplantation
Diabetes mellitus	• Requiring medications, including insulin injections
Immunosuppression	• Due to disease or treatment, i.e. HIV infection; systemic steroids for more than a month at a dose of prednisolone >20 mg per day; asplenia or splenic dysfunction; etc.

LEARNING POINTS

- **Influenza is caused by a segmented RNA virus with the ability to reassert the viral genome. The combination of mutations (antigenic drift) and reassortment (antigenic shift) explain both the lack of lifelong immunity to infection as well as the potential for pandemic influenza to occur.**
- **Specific antiviral therapy such as oseltamivir can be prescribed for persons with confirmed or strong clinical suspicion for influenza, particularly those belonging to the population subsets listed in Table 1.**
- **Influenza vaccinations are safe and help to reduce the risk of influenza at both individual and population levels. Annual vaccinations are currently recommended for all persons above the age of two years, even for those with severe egg allergy.**