A New Framework for Influenza—Rational Use of Antiviral Therapy and Vaccines

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Abstract

Seasonal influenza is a major health burden worldwide and pandemics have the capacity to stress the healthcare system severely. During the last pandemic of influenza in 2009—the first in decades—many new tools were utilized in the management of influenza. The employment of these resources constitutes a new paradigm and framework for understanding and responding to both seasonal and pandemic influenza.

Keywords

Influenza, vaccine, antivirals

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Influenza kills approximately 3,000 to 49,000 Americans per year[1] and the potential for a pandemic—as seen in 1918, 1957, 1968, and 2009—looms large and has prompted the US government, healthcare facilities, and healthcare workers to undertake extensive pandemic preparation. Activities include hospital planning, vaccination schedules, as well as antiviral medication stockpiling. To this last end, the US government has developed a Strategic National Stockpile (SNS) of antiviral medications for use during a pandemic for treatment as well as prophylaxis.

However, clinical practice with seasonal influenza is varied and falls short of the competence needed in a pandemic or severe seasonal outbreak, as evidenced by several cases in which antiviral therapy administration to patients was delayed during the 2009 H1N1 pandemic.[2] Moreover, the current state of resistance of both H1N1 and H3N2 influenza A isolates to various classes of drugs has become cumbersome for clinicians to comprehend and the knowledge of some virulence-enhancing features of influenza strains is not well known to clinicians. This review will present some of the most important new developments in the clinical management of influenza.

Current Clinical Practice for Testing and Treating Influenza

Testing

Most hospitals have the availability, on-site, for rapid detection of influenza A or B virus antigens from nasopharyngeal swabs and some larger institutions use highly sensitive polymerase chain reaction (PCR)-based methods. Yet many clinicians do not use these tests for a variety of reasons, including a perceived lack of effect on medical decision-making.[3] Indeed, Centers for Disease Control and Prevention (CDC) recommendations reinforce that testing should be done only when it will affect medical decision-making. Also, given the 48-hour window for maximal antiviral efficacy, many people fail to present rapidly enough to receive maximum benefit from treatment, making diagnosis seem somewhat superfluous. Additionally, some small hospitals outsource their influenza testing to bigger hospitals or laboratories (eliminating the availability of real-time results).

Several factors—other than the relative insensitivity of rapid antigen testing—are overlooked for the reasons cited to forgo rapid testing.

- The ability to distinguish clinical cases of influenza from other respiratory viral illnesses is poor.[4] What may or may not be labeled 'influenza' could be another similar illness.
- If a patient presents outside the treatment window, they remain infectious and diagnosis of influenza will influence isolation procedures (if the patient is admitted) or prophylaxis decisions for household contacts (e.g. cohabitation with an immunosuppressed individual). Of note, a nosocomial case of influenza is responsible for $3800 in extra charges per patient.[5]
- Data indicate that oseltamivir, given outside the 48-hour window, can prevent some of the serious sequelae of influenza infection as well as reduce shedding of the infectious virus.[6]
- A diagnosis of influenza can often delimit a work-up for illness by providing a diagnosis and prevent the unnecessary prescription of antibiotics, even when tests without 100% sensitivity are utilized.[7,8]

Treating

Prior to the 2009 H1N1 pandemic, the use of antiviral therapy for influenza infections was relatively low in the US.[9] With the data accumulated during the pandemic, guidelines have now become more

Table 1: Indications for Antiviral Therapy

Antiviral Recommended
Severe, complicated, or progressive illness
Hospitalization
High risk for complications • Age <2 years or >65 years • Pulmonary, cardiovascular, renal, hepatic, hematologic, neurologic, metabolic conditions (including diabetes), immunosuppression, pregnant or post-partum state, age <19 on long-term aspirin therapy, Alaskan Natives, Native Americans, body mass index >40, residents of chronic-care facilities
Antiviral Treatment Considered
Any previously healthy, non-high-risk, symptomatic outpatient with confirmed or suspected influenza based upon clinical judgment, if treatment can be initiated within 48 hours of illness onset

Table 2: Drug Resistance by Genetic Mutation

Mutation	Resistance Conferred
H274Y/H275Y (NA gene)	Confers resistance to oseltamivir with cross resistance to peramivir; widespread in seasonal H1N1 (pre-2009), seen in isolated cases of 2009 H1N1 and H5N1
S31N (M2 gene)	Confers resistance to adamantanes; seen in virtually all H3N2 and 2009 H1N1 isolates
Q136K (NA gene)	Confers resistance to zanamivir; very rare; cross-resistance to peramivir

Table 3: Vaccine Type, Dose and Age Indication

Vaccine Type	Age Indication
Standard trivalent inactivated injectable vaccine (45 µg)	All ages
Live-attenuated trivalent nasal spray vaccine (FluMist™)	Ages 2–49
High-dose trivalent inactivated injectable vaccine (FluZone High Dose™, 180 µg)	Age >65
Intradermal trivalent inactivated injectable vaccine (Fluzone intradermal, 27 ug)	Ages 18–64

supportive of the use of antiviral drugs and clinicians are now more familiar with the options for treatment. Current guidelines for the 2010–2011 influenza season emphasize certain high-risk groups who should always receive antiviral treatment, irrespective of whether presentation is outside the 48-hour 'window' and other groups in whom to consider antiviral therapy (see *Table 1*).[10] Treatment initiation should not wait for influenza confirmation, especially in any high-risk group for which antiviral therapy is indicated.

The Antiviral Agents

The Adamantanes

Amantadine and rimantidine, members of the adamantane class of antiviral drugs, which block the function of the influenza M2 protein, have largely been supplanted because of the near-universal resistance of H3N2 and 2009 H1N1 to this class of agents. Moreover, adamantanes have no activity against influenza B.[11]

Neuraminidase Inhibitors

There are two neuraminidase inhibitors available in the US (oseltamivir and zanamivir) and two additional agents are available in Japan (peramivir and laninamivir).[12] Neuraminidase inhibitors are active against both influenza A and B and are the mainstay of treatment for influenza. The main limitation with both oseltamivir and zanamivir are their modes of delivery. Oseltamivir is available only in an oral formulation while zanamivir is available solely via the inhalational route.[13] Because of these limitations, during the 2009 H1N1 pandemic, an intravenous formulation of peramivir was used via an Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA).[14] Additionally, intravenous zanamivir was available via 'compassionate use'.

The duration of treatment with neuraminidase inhibitors is generally five days for treatment and seven days after exposure for prophylaxis (at a reduced dose).[15] However, in severe cases longer treatment duration and higher administered dosages have been advocated, sometimes guided by the duration of influenza PCR/culture positivity.[16]

Ribavirin

Used in the treatment of hepatitis C and respiratory synctial virus (RSV)—two other RNA viral diseases—the nucleoside analog ribavirin is known to have activity against influenza A and B and was once submitted for FDA approval for that indication. Robust studies detailing its efficacy are lacking, however it has been used for influenza treatment in its oral, inhalational, and intravenous (via an investigational drug application) forms for influenza. Its side-effect profile (hemolytic anemia and teratogenicity) will likely preclude its widespread use.[17]

Combination Therapy

Although it has not been studied in randomized controlled trials, dual therapy with agents from both the adamantane and neuraminidase inhibitor class has been used successfully and advocated in cases with the highly fatal H5N1 avian influenza strains.[18] More recent data using both oseltamivir and zanamivir have not shown benefit for dual use.[19] A triple-combination pill containing amantadine, ribavirin, and oseltamivir is also under development.[20]

Influenza Antiviral Resistance as a Distinct Discipline

As has become apparent with HIV, resistance testing and understanding of genotypic implications for treatment decisions can become very complex. Influenza's myriad subspecies, clades, and subtypes make it difficult for healthcare providers to keep abreast of which drug is best for which virus. One hundred per cent oseltamivir resistance in H1N1 isolates with 100 % adamantane sensitivity juxtaposed with the opposite scenario in H3N2—the situation pre-2009 H1N1—is difficult for clinicians to comprehend and consequently can have a deleterious effect on prescribing practices. Use of resistance testing, similar to the paradigm of HIV, is needed.[21] Of the many mutations that can confer resistance to antiviral agents in influenza, three antiviral mutations in influenza merit close study by clinicians (see *Table 2*).[22,23]

Neuraminidase Inhibitor Resistance Explained

Neuraminidase inhibitors are all derived from a parent compound known as 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA), which binds avidly to the viral neuraminidase active site. Oseltamivir includes two modifications from the DANA structure that require an active site conformation change for binding. This area is a site of

resistance mutations (e.g. H275Y). Zanamivir has one modification from the DANA structure and is, therefore, less susceptible to resistance, while peramivir cross-resistance occurs in oseltamivir-resistant viruses because peramivir and oseltamivir are similar in structure.[24]

Influenza Vaccination is Now Universally Recommended

For the upcoming season, influenza vaccine is now recommended for all age groups greater than six months. Prior season vaccination rates have varied, with the most recent season showing a median uptake rate of approximately 40 % for the seasonal vaccine and 24 % for the 2009 monovalent H1N1 vaccine.[25,26]

Four Formulations of Influenza Vaccine are Available

There are currently four different unadjuvanted vaccines available in the US (see *Table 3*).[27,28] The live-attenuated vaccine has shown greater efficacy in younger age cohorts and should be the preferred vaccine for that age group.[29] Likewise, immunogenicity studies in the elderly, administered the high-dose formulation, indicate that its greater efficacy may make it the preferred vaccine for that age group.[30] The intradermal version of the vaccine includes a lower antigen dose and is administered with a shorter needle.[28]

Virulence Enhancing Features of Influenza

Several virulence-enhancing features of influenza have been identified and are known to increase morbidity and mortality from influenza. They are summarized in *Table 4*.[31–33]

Adjunctive Therapies

Given the current interest in immunomodulatory therapy, several different immunomodulatory drugs have been considered for use in influenza. Though there are no randomized human clinical trials to support their use, HMG-CoA reductase inhibitors ('statins'), cycloxygenase-2 inhibitors (celecoxib), and peroxisome proliferator-activated receptor (PPAR) agonists (metformin, pioglitazone, gemfibrozil) have been advocated as adjuncts to standard therapy to restrict the inflammatory response from influenza.[34] There also may be some benefit to the administration of intravenous immunoglobulin (IVIG) or convalescent sera as well.[35,36]

Table 4: Virulence-enhancing Features of Influenza

PB1-F2[30,31]
A pro-apoptic toxin produced from an alternate open reading frame of the PB1 gene; present in most avian and human isolates; absent from 2009 H1N1
Polybasic amino cleavage site of viral hemagglutinin[31,32]
Proteolytic cleavage site of viral hemagglutin that, when containing basic amino acids at site, allows for greater organ tropism owing to ability to be cleaved by alternative protease; seen in highly pathogenic avian influenza viruses (e.g. H5, H7)
D225G[32,33]
Mutation in hemagglutinin that confers the ability of an influenza virus to bind to the alpha 2,3-sialic acid containing cells in the lower respiratory tract

Strategies for Optimizing Treatment of Concomitant Bacterial Pneumonia

During the 2009 H1N1 pandemic bacterial pneumonia complicated up to 55 % of cases of influenza necessitating the use of antibacterial therapy.[37] New data are emerging—from animal models—that choosing antibacterial agents that have some immunomodulatory properties may be beneficial. Data suggest that the use of cell-wall active agents alone releases inflammatory molecules that, through a TLR-2 dependent pathway, enhance inflammation. The use of combination therapy including azithromycin, even in the setting of azithromycin resistance, may be useful in quieting inflammation. Also, animal data suggest that clindamycin may have a lesser—but still significant—benefit.[38]

Conclusion

Adept management of seasonal influenza, employing the latest technologies and clinical thinking, carries almost 100 % applicability to a pandemic situation, where the efforts would be scaled up to a nationwide level. Implementation of widespread influenza testing, typing, and informed antiviral prescribing will create an environment much more resilient and adept at managing influenza, rendering a pandemic influenza virus spread much more difficult. The expertise and competence engendered by a program, to increase clinical and laboratory acumen with seasonal influenza, will add to the confidence with which pandemics are approached and will supplement pandemic readiness measurably. ■

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