Use of antiviral medication and stockpiling Issues *Karen Green RN, MSc*

Vaccines are always the best protection from influenza, but it is unlikely that a vaccine against the new pandemic strain of influenza will be available during the early stages of a pandemic. During this period, the use of antiviral medication must be carefully evaluated.

Antiviral medications effective against current influenza strains are effective against pandemic strains *in vitro*, and will likely provide substantial protection. Resistance is a potential issue, but is unlikely to be a significant problem for the next few years. There are drawbacks to the use of antiviral medication. Antivirals only provide protection while a person is taking them. Thus, if antivirals run out before a vaccine is available, everyone is at risk, and the pandemic impact may only be delayed. Long term use might also have side effects that we have not yet identified. There are several ways that antivirals may be used in a pandemic.

Continuous prophylaxis

Use of antiviral medication by uninfected individuals for the duration of influenza activity (probably 50-100 days) is an effective option, but one that requires large stockpiles. This option is not feasible for the general population, because such supplies cannot be obtained; it is also not cost-effective in most pandemic scenarios. Long-term prophylaxis may be beneficial in groups in whom minimizing absenteeism during a pandemic is critical, eg. healthcare professionals.

Postexposure prophylaxis

Close contacts of an individual with influenza could be treated with antiviral medication after exposure but before the onset of symptoms. This strategy, if used in conjunction with immediate isolation of the ill person, might reduce transmission once a case has been identified, and permit close contacts to care for that person at home. This strategy's effectiveness depends on the ability to quickly identify cases and their contacts, since the generation time of influenza (average time from onset of symptoms in one case to onset in the second case) is only 2 days. For the foreseeable future, there are insufficient supplies of neuraminidase inhibitors to attempt this strategy.

Treatment

There is good evidence that early treatment with oseltamivir is effective in reducing the duration and severity of influenza, and the risk of serious complications, including hospitalization. It seems likely that treatment of pandemic influenza will also be effective. Early treatment is more effective than later treatment, so attempts will be made to start everyone with compatible illness on therapy within the first 48 hours after symptom onset. There is no doubt that this will be difficult, since so many people will be ill simultaneously. Additional problems with this strategy are that treatment for influenza is much less effective than prophylaxis, and many treated people will likely get complications. At the moment, government stockpiles are targeted to treatment of 10% of the population at currently recommended doses. It is estimated that about 35% of people will develop influenza, and likely that higher doses and longer duration of therapy will be needed for pandemic influenza. Our stockpiles for therapy are still inadequate if the pandemic is moderate or severe.

Individual Stockpiling versus Government Stockpiling

Public health stockpiling of anti-viral drugs for an influenza pandemic is viewed as an appropriate and cost-effective strategy. The disadvantages of individual stockpiling are:
(i) When shortages exist, centralized decision making gives us the best chance of allocating drug in a way that minimizes mortality and morbidity;
(ii) Individual stockpiling may result in inappropriate use of the medications.

So we are faced with the dilemma. It is clear that individuals are better off with a stockpile, but it is also clear that society is better off if the supply is centralized. In addition, there is a lack of consensus about what an optimal stockpile size is, with some physicians believing that currently planned Canadian government stockpile sizes (enough to treat 10% of the population) are too small.

Thus, physicians have found themselves bombarded with requests for oseltamivir prescriptions. In the absence of clear directives or recommendations on how to respond to these requests, physicians find themselves in a struggle between their responsibility to their patients and their responsibility to the public good. In the fall of 2005, Roche decided to stop sales to private pharmacies in North America. In late January, this ban was lifted in the United States, but not in Canada.

The best each of us can do is to offer 'credible' explanations to patients seeking drugs for personal stockpiles. Patients are rational in wanting their own stockpile and society is rational in not wanting them to have it. As long as oseltamivir remains in short supply, there is only one really legitimate argument against personal antiviral stockpiles. That is, that society as a whole will be better off if the entire supply is centrally controlled for optimal use. In order to support this argument, however, each of us needs to be educated about the potential uses of oseltamivir, to make a decision about what the size of our stockpiles should be for Canada, and to lobby our professional organizations, local public health units, and governments to ensure that these stockpiles exist.

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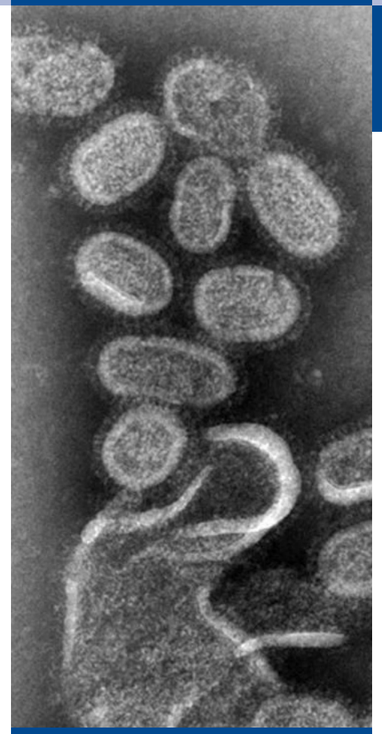

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TIBDN
TORONTO INVASIVE BACTERIAL DISEASES NETWORK

Pandemic influenza update *Allison McGeer, MD*

In January, 2006, the first A/H5N1 influenza cases outside of Southeast Asia were reported from Turkey. The bad news is that this virus has rapidly become widespread in wild waterfowl and chickens throughout Turkey. There may be as many as 30 human cases, still with a high mortality rate. The hemagglutinin protein of the viruses isolated from Turkey has changes that make it closer to a human virus than ever before. The good news is that there has been no human to human transmission identified in Turkey, and that control measures being implemented there seem to have been effective in slowing the number of new human cases.

Our knowledge about influenza viruses and influenza infection is growing rapidly. Nonetheless, it remains impossible to predict whether H5N1 will be the cause of the next pandemic. We do know that the time to the next pandemic gets shorter every day, and our chronic shortages in health care combined with our "just-in-time" delivery system will mean that even a mild pandemic will severely stress the system.

Both Health Canada and the Ontario Ministry of Health will be releasing new versions of their pandemic plans later this spring. Many local health units have first versions of their plans, and most hospitals are also working on plans. It is also time for physician offices, pharmacies, and clinics to start preparing. While the Ontario Ministry of Health is building stockpiles of personal protective equipment, they are expecting that individual offices and hospitals will also contribute to their own protection. A list of supplies that offices and clinics should consider stockpiling is shown in the box: each office should have enough to manage for 4-6 weeks. Clinics should also consider how they will separate influenza patients from non-influenza patients (it may be a good idea to consider "shared" clinics or triage sites in cooperation with local hospitals and public health, where physicians and other staff contribute hours), and how to start providing patient teaching about preventive practices and home management of influenza.

Suggested supply list for offices and clinics

Alcohol handwash
Fluid resistant masks
Eye protection
(eg. 2 pairs safety glasses per person)
Gloves
Surface cleaning supplies
Re-useable thermometer

Pandemic Influenza Planning

Canadian Pandemic Influenza Plan:
http://www.phac-aspc.gc.ca/cpip-pclcpi

Ontario Health Plan for an Influenza Pandemic:
http://www.health.gov.on.ca/english/providers/program/emu/pan_flu/pan_flu_plan.html

Toronto Pandemic Influenza Plan:
http://www.toronto.ca/health/pandemicflu

Public Safety Canada:
http://www.safecanada.ca/pandemic

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What' s new in seasonal influenza?

Allison McGeer, MD

Although much of our attention is focused on when the next influenza pandemic will emerge, annual epidemics of influenza continue to cause thousands of deaths and hospitalizations in Canada.

Last year's influenza season began early in January in Ontario, with activity peaking in the first week of February. Most influenza was due to A/H3N2, and a mid-season shift in the virus meant that most infections in February and March were caused by a new variant called A/H3N2/ California/7/2004. Fortunately, there was sufficient cross-reactivity between this new strain and the H3N2 strain in the vaccine (A/Fujian/411/2002) that the vaccine still provided protection. Some experts believe that the apparent increase in the speed of evolution of new virus strains presages the next pandemic.

So far this year, there has been little influenza activity in Ontario. Most influenza to date in Canada has occurred in Alberta and BC. In Alberta, most isolates have been influenza B, and several school outbreaks have been reported. In contrast, in BC, most of the infections have been influenza A/H3N2 (so far, all the A/California/7/2004 strain).

Over the last few years, two different groups of influenza B strains have evolved. For the last few years, the major influenza B strain has been of the "Shanghai" lineage, with a smaller number of isolates of the "Hong Kong" lineage. The 2003 and 2004 vaccines had antigen from the Hong Kong type viruses; because the Shanghai type viruses were increasing in frequency, the 2005 vaccine antigen was changed to a Shanghai like one. However, this year so far, most of the B viruses have been Hong Kong-like strains that this years vaccine will not be very effective against. Those people who have had a vaccine in previous years will likely still have substantial protection.

The other significant change this year has been the emergence of resistance to amantadine in influenza A/H3N2 viruses. Amantadine resistance emerges quite easily in patients who are on treatment for influenza; however, it has remained otherwise rare until very recently. In Canada, until 2003, all isolates of influenza A were susceptible to amantadine (note: influenza B is intrinsically resistant). However, amantadine resistance has now emerged and spread rapidly, This year, more than 90% of the influenza A isolates tested in Canada have been resistant to amantadine. Both Health Canada and the US Centers for Disease Control and Prevention have recommended that only neuraminidase inhibitors (oseltamivir and zanamivir) be used for treatment or prophylaxis of influenza.

Laboratory confirmed influenza illness requiring hospital admission: Clinical features, treatment, and outcomes

Allison McGeer, MD

It is important before the pandemic that we understand as much as possible about the clinical features and complications of influenza, as well as the impact of treatment with antivirals. For this reason, the Toronto Invasive Bacterial Diseases Network (TIBDN) has begun population-based surveillance for laboratory-confirmed influenza illness (LCII) resulting in hospital admission in residents of our population area (metropolitan Toronto and the regional municipality of Peel)

A case of influenza requiring hospital admission is defined as a patient whose illness requires hospitalization, and who has a positive antigen test or a culture yielding influenza A. Patients who acquire influenza while in hospital are also included. Clinical data is collected by chart review, and interview with patients, attending and family physicians.

During the 2004/5 influenza season, 403 patients were hospitalized due to lab-confirmed influenza. Thus, during the first five months of 2005, more patients were hospitalized for lab-confirmed influenza than for invasive pneumococcal disease. There was a great deal of variability in the number of diagnosed cases per hospital: hospitals rarely doing NP swabs identified few cases: the two hospitals routinely testing adults with respiratory illness (Credit Valley and William Osler Health Centre) diagnosed 221 and 82 cases, respectively.

Of the 403 patients, 102 (25%) were children (aged 15 years of age and under), 73 (18%) were adults aged 16-64 years of age, and 228 (57%) were adults over the age of 65 years.

Most infections, 291 (78%), were due to influenza A, with 112 (22%) to influenza B. Influenza B infection was more common in children (50/102, 49%) than adults aged 15-64 years (21/73, 28%), or older adults (41/228, 18%), P<.001.

Clinical characteristics, treatment and outcomes of disease are shown in Tables 1 and 2. Most children and nearly half of adults aged 50-64 years of age had no significant underlying illness; however, more than 25% of adults aged 15-64 years were smokers. A very significant proportion of infections were acquired in nursing homes, or in the hospital – this is not because influenza is more common in hospitals and nursing homes, but because diagnostic testing is done more commonly in these circumstances.

Overall, none of the 102 children, and 112 of 289 adults (39%) were treated with oseltamivir. Oseltamivir was prescribed more often to patients with nosocomial and nursing home acquired disease (P<.001), older patients (median age 78y vs 57y, P<.001), and patients with chronic underlying illness (38/114 with Charlson scores of >2 vs 50/ 275, P=.002).

Current recommendations are that antivirals should only be initiated within 48 hours of the onset of symptoms: in this cohort, most patients were treated later. Only 13/54 (24%) adults with community-acquired disease, 9/22 (41%) with nursing home acquired disease, and 20/36 (55%) with nosocomial disease had their first dose of oseltamivir within 48 hours of symptom onset. Nonetheless, treatment with oseltamivir appeared to be associated with a substantial reduction in mortality. In multivariate analysis, factors associated with survival were younger age (OR 4.1, 95% CL 1.1,15), residence in the community rather than a nursing home (OR 4.9, 95% Cl 1.8,14), and therapy with oseltamivir (OR 3.1, 95% CL 1.03,10).

More than half (53%) of patients with community-acquired illness had a physician visit before their admission. Twenty-four percent of patients were started on an antibiotic, while less than 1% were started on antiviral therapy

Comments

These data illustrate that, despite that more than 40% of people in Ontario receive influenza vaccine every year, influenza is still an important disease. Current vaccines substantially reduce the mortality associated with influenza (for adults over the age of 65, vaccination is associated with 42% reduction in all cause mortality during influenza season). However, there is enough residual disease that better diagnosis and treatment remain important.

These data confirm data from randomized controlled trials that oseltamivir therapy is associated with a very significant reduction in serious complications and mortality due to influenza. Further, they suggest that if a patient is shedding virus at admission (that is, has a positive rapid antigen test), treatment is effective even if the patient has been symptomatic for more than 48 hours. During influenza season, all patients who require admission and have symptoms of respiratory infection should have a rapid test done for influenza, and should be treated with oseltamivir (or zanamivir) if the test is positive.

Physicians should also think about replacing empiric antibiotics with empiric antivirals when out-patient therapy of respiratory illness is being initiated during influenza season. Although we tend to think of using antibiotics in patients we are worried about to protect them from complications, the data from TIBDN surveillance suggests that antivirals may actually be more effective at preventing serious complications and hospitalization.

Finally, 13% of influenza cases identified by surveillance were hospital acquired, and two of 59 patients with hospital-acquired influenza died from their infection. The identified rate of hospital acquired influenza in TIBDN last year was still 5 to 10 times lower than that identified in other prospective studies where testing was routine, suggesting that our detection of hospital-acquired influenza cases is poor. Most patients at risk of acquiring influenza in the hospital are elderly and have comorbid illnesses. Such patients are also likely to benefit from early antiviral therapy. During the influenza season, we should be alert to hospital –acquired respiratory disease in patients, test them promptly, and treat those patients who have influenza.

Table 1: Clinical characteristics of patients with LCII requring hospitalization

	0-14 years (n=102)	15-64 years (N=73)	65+ years (N=228)
Underlying illness			
None	77/101 (76%)	31/72 (43%)	32/220 (15%)
Lung disease	17 (17%)	22 (31%)	83 (38%)
Diabetes mellitus	-	17 (24%)	108 (49%)
Cardiac disease	1 (1.0%)	8 (11%)	149 (68%)
Renal disease	-	8 (11%)	29 (13%)
Cancer	2 (2.0%)	3 (4.2%)	24 (11%)
Other	4 (4.0%)	7 (9.7%)	8 (3.6%)
Current smoker	-	20/72 (28%)	15/220 (6.8%)
Source of infection			
Community	101 (99%)	57 (78%)	135 (59%)
Nursing home	-	4 (6%)	47 (21%)
Acute care hospital	1 (1%)	12 (16%)	46 (20%)

Table 2: Treatment & outcomes of patients with LCII requiring hospitalization

		Adults		
Source	Children (N=102)	Community (N=181)	Nursing Home (N=50)	Hospital (N=58)
Antiviral treatment				
Amantadine	0	1 (0.6%)	1 (2%)	0
Oseltamivir	0	54 (30%)	22 (44%)	36 (62%)
Antibacterial treatment	75 (74%)	146 (81%)	46 (92%)	35 (60%)
ICU Admission	2 (2%)	27 (15%)	9 (22%)	N/A
Hospital LOS (median, range)	2 (1-10d)	6 (1-103d)	10 (1-47d)	N/A
Death due to influenza	0	12 (6.6%)	9 (18%)	3 (5.2%)