AAEM Clinical Practice Committee Statement

The Pertinent ED Information Concerning the Vaccination Efficacy, Sensitivity of Diagnostic Testing, and Role for Antiviral Medications for Seasonal Influenza (1/12/2015)

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Introduction:

Influenza is an acute respiratory virus that is responsible for both epidemic and pandemic outbreaks of disease. There are three types of Influenza (A, B, and C) that are further subtyped based on surface proteins. Currently, A (H1/N1) and A (H3/N2) are the subtypes circulating in humans (1). The annual global prevalence of seasonal influenza is estimated at 5%–10% in adults and 20%–30% in children (2). Worldwide, influenza infection is estimated to result in about 3 to 5 million cases of severe illness, and an estimated 250,000 to 500,000 deaths (2). This clinical practice guideline will address three main topics of influenza including vaccination, diagnosis, and treatment.

Executive Summary

1. Meta-analyses of vaccination efficacy (VE) demonstrate approximately 60% VE (with the potential for significant variability from year to year). Studies including elderly or chronically ill patients have significant flaws that limit conclusions in this demographic. However, vaccination in this population is clinically warranted due to higher morbidity and mortality from influenza.

2. A negative rapid antigen detection test in the emergency department (ED) has insufficient sensitivity to exclude influenza. In the proper clinical setting, treatment should proceed as if the patient has tested positively.

3. Treatment with oseltamivir reduces time to alleviation of first symptoms by approximately 16 hours in adults and healthy children but does not reduce the rate of hospitalization. There is little benefit of prescribing oseltamivir to dischargeable ED patients other than to provide prophylactic administration to household contacts of confirmed patients.

Question 1: What is the efficacy of the seasonal influenza vaccine in preventing influenza and disease-related morbidity?

Influenza vaccines are prepared annually and targeted at the most probable circulating strains. As a result, VE is closely linked to how well the vaccine is matched to circulating strains. Current studies demonstrate significant heterogeneity in quality, inclusion criteria, diagnosis of infection, and definition of end-points. In 2012, Diazgranados et al published one of the largest meta-analyses to date, comprising 88,468 patients (3). Eligible patients included healthy children and non-elderly adults. The clinical end-point was an occurrence of influenza-like symptoms combined with laboratory confirmation (e.g. PCR, culture) of disease. Diazgranados et al reported a summary VE of 65% against any strain, but slightly higher VE (78%) against matched strains. However, no morbidity or mortality benefit was mentioned in this analysis. Other meta-analyses by Manzoli et al in 2012 and Osteholm et al in 2012, also reflected an overall VE of around 60% in healthy non-elderly adults (4, 5). The Cochrane review in 2012 of VE in the elderly stated that the available literature was too varied and inadequate in quality to make any conclusions about VE in this demographic (6). However, from a clinical standpoint, there is no debate on the potential for severe illness due to influenza infection in the elderly therefore vaccination in this age group will remain a priority.

Question 2: What is the most effective way to test for influenza in the ED setting?

The CDC recommends testing for influenza only when the results of the test will impact patient treatment. If testing is warranted, testing for influenza in the ED has traditionally relied upon rapid antigen detection (RAD). Sensitivity depends heavily on the quality of the specimen, strain of influenza, viral titer (i.e. amount of virus being shed), duration of illness, and collection technique. Numerous studies have shown that sensitivity varies widely but generally falls within the 40-80% range for seasonal influenza and is even worse for H1N1 (40-60%) (7-9). It is imperative to recognize that a negative RAD does not exclude influenza and treatment should proceed as if the patient had tested positively. Viral culture had long been considered the gold standard for diagnosis but it takes at least 48 hours thus limiting its ED utility. Nucleic acid detection (RT-PCR) has emerged in the past decade as the diagnostic test of choice for influenza and has been shown to have improved sensitivity and specificity when compared to viral culture. Sensitivity and specificity of RT-PCR approach 100% and are limited only by collection technique and viral titer (10).

Question 3: What is the clinical effectiveness of antiviral treatment on treatment and prophylaxis of seasonal influenza?

Currently there are two classes of medication approved for seasonal influenza, amantadines and neuraminidase inhibitors (NI). It is commonly accepted that there is widespread resistance to amantadines, and therefore, treatment with neuraminidase inhibitors have been widely promoted as beneficial to patients. The largest collection of data is from the Cochrane collaboration. The recently published review from Jefferson *et al* utilized study reports of all randomized control trials (RCT) both published and unpublished (11). This data was obtained directly from the pharmaceutical industry in their supported trials. The authors evaluated 46 studies and found a large amount of attrition, reporting, and attention biases. However, based

on this data they concluded that oseltamivir and zanamivir decreased time to the alleviation of first symptoms by 16 and 12 hours respectively. Neither drug reduced the rate of hospitalization in either adults or healthy children (11). The next question that must be answered is the efficacy of prophylactic antiviral use on transmission of influenza. The data shows that prophylaxis does prevent transmission of disease with a number needed to treat for benefit of 33 and 51 for oseltamivir and zanamivir respectively (11). The use of NI, mainly oseltamivir, does have some adverse effects that should be considered when prescribing the medications. Oseltamivir is associated with higher rates of nausea, vomiting, and headaches (11, 13-16). In summary, use of NI provides marginal benefit in decreasing during of symptoms and reduction in transmission of disease. We do recommend that clinicians continue to follow CDC guidelines that state NIs should be used for patients that are hospitalized, are at higher risk for complications and have severe, complicated or progressive illness.

In conclusion, influenza is a complex virus with studies that suggest vaccination is far from 100% efficacious and that treatment with NIs is expensive yet offers marginal benefit to patients. In addition, testing in most EDs relies on the rapid antigen test that suffers from poor sensitivity. However, there is little question that influenza poses a significant annual health threat to an at risk population (e.g. elderly, immunocompromised, very young) and the drawbacks of vaccination and aggressive treatment are minimal other than cost to the healthcare system.