

Occasional review: Influenza in COPD: pathogenesis, prevention, and treatment

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Abstract: Influenza viruses cause respiratory tract infections that in patients with underlying lung diseases such as chronic obstructive pulmonary disease (COPD) are associated with exacerbations and excess morbidity and mortality. Typically, influenza B is associated with relatively mild, local outbreaks, whereas influenza A is the cause of world-wide pandemics. Upon infection, two antigens present on the viral surface, hemagglutinin and neuraminidase result in human immunity, but since many subtypes of these antigens exist that vary over time, immunity in the population is blunted. Vaccination is advocated in high-risk groups including patients with underlying (lung) diseases and in the elderly, and needs to be repeated annually with vaccines expected to cover the expected change in viral antigenicity. When started early, antiviral drugs, especially neuraminidase-inhibitors can be prescribed in adjunct to nonspecific interventions in an attempt to shorten disease duration and to prevent complications in case of an influenza infection. Currently, the effectiveness of antiviral drugs specifically in patients with COPD has not been proven.

Keywords: influenza, chronic obstructive pulmonary disease, COPD, neuraminidase inhibitors, prevention, treatment

Introduction

It is believed that the risk of a pandemic outbreak of influenza is growing. Three pandemics occurred in the 20th century; most recently in 1968 which resulted in millions of deaths worldwide. A new outbreak may have similar devastating results and is likely to affect elderly people, patients with reduced immunity, and patients suffering from chronic diseases such as chronic obstructive pulmonary disease (COPD).

Chronic obstructive pulmonary disease is characterized by largely irreversible progressive airflow limitation. This airflow obstruction is associated with an inflammatory process in the bronchial mucosa. Most patients are current or ex-smokers. Many patients have one or more exacerbations per year, which are associated with an accelerated decline in lung function and decreased quality of life (NHLBI 2006). Exacerbations are responsible for over half of the direct disease-related costs of care. Viral infections including influenza, respiratory syncytial virus (RSV), and many other viruses are important causes of exacerbations, excess morbidity and mortality in COPD (Wedzicha 2004; Wilkinson et al 2006). During seasonal outbreaks of viral infections, patients with COPD are at risk for respiratory illness-related hospitalizations, irrespective of age or disease severity (Gorse et al 2006). Prevention and early treatment of exacerbations are therefore believed to be an important target in the management of COPD. Inhaled steroids may reduce the number and the severity of exacerbations in patients with severe airflow obstruction and frequent exacerbations, but the effects are limited (Burge et al 2000; Jones 2004). Inhaled bronchodilators may have similar effects. Annual influenza vaccination is recommended in most COPD guidelines and neuraminidase inhibitors are available for the treatment of influenza.

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Evidence of the role of influenza viruses in the pathogenesis of COPD and as a cause of exacerbations is discussed in this review and current recommendations for prevention and treatment of influenza in patients with COPD are summarized.

Influenza viruses

The influenza virus belongs to the orthomyxovirus group. The influenza virus is a spherical or filamentous enveloped virus. Virus strains are characterized by different hemagglutinin (H) and neuraminidase (N) subclasses. Hemagglutinin, a surface glycopeptide, aids attachment of the virus at specific receptor sites on the walls of susceptible host cells and facilitates entry of viruses into the cell. The enzyme neuraminidase facilitates cell penetration by pinocytosis and stimulates the release of viruses from the host cell by budding through the cell membrane (Matrosovich et al 2004). The virus exists in two main forms: A and B. Influenza A is generally responsible for epidemics and pandemics. Influenza B causes milder, generally more localized and less severe outbreaks, eg, in schools or in camps. A lesser known C form rarely causes disease in humans. 15 H subtypes (H1–H15) and nine N subtypes (N1–N9) have been identified for influenza A viruses. New antigenic variants of influenza A develop at irregular intervals through the process of antigenic shift, whereas point mutations in influenza A and B viruses result in changes in amino acids in the H and the N glycoproteins responsible for humoral immunity, resulting in antigenic drift (Zambon 1999). These changes render the individual's immune response less able to combat new variants. As a result, major shifts in antigenic profiles of the viruses can cause epidemics. The immune system is less blunted by the minor antigenic drifts that cause less severe outbreaks (Stambouliau et al 2000). In 1957 the appearance of influenza A2 type H2–N2 was associated with over 20 million deaths. The worldwide pandemic that occurred in 1968 was the result of the emergence in Hong Kong of influenza H3–N2. Minor antigenic drifts have since then caused smaller outbreaks in various areas of the world. Avian flu, caused by H5–N1, has emerged in 1997 and re-emerged in 2004–2005 and represents a major change in viral surface antigens, and transmission to humans has been shown to be a serious threat (Beigel et al 2005).

Influenza infections

Influenza is thought to occur in approximately 20% of the world's population annually. In most cases influenza is an acute febrile respiratory disease that occurs in annual outbreaks of varying severity. The incubation period of

influenza is 1 to 3 days. Influenza typically causes extensive destruction of airway epithelial cells (Hers 1966). Symptoms start abruptly and consist of fever, shivering, and diffuse pains in the extremities. Many patients present with early, prominent systemic symptoms and have headache, soreness of the throat, and dry cough that can persist for several weeks (Monto et al 2000). Mortality can be high in the elderly especially in patients with chronic respiratory or cardiac diseases. Recovery can take up to 3 months and secondary bacterial infections are common, particularly with *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Staphylococcus aureus* superinfections can cause pneumonia that has a mortality of up to 20% (Brundage 2006).

In otherwise healthy individuals, treatment consists of paracetamol, bed rest, and sufficient oral intake of fluids (Wiselka 1994). In patients with COPD, as in patients with heart or kidney diseases, early treatment with appropriate antibiotics is recommended (Nathan et al 2001).

Role of influenza in stable COPD and in exacerbations

In susceptible persons, usually smokers, exposure to inhaled noxious particles and gases results in inflammation in the bronchial mucosa, lung parenchyma, and pulmonary vasculature (NHLBI 2006). Other processes believed to be of importance are an imbalance of proteinases and antiproteinases and oxidative stress. Many cells and mediators are involved in the pathogenesis of inflammation in COPD. With time this inflammation can result in structural changes in the bronchial wall and destruction of lung parenchyma or emphysema, and consequently in irreversible airflow obstruction and gas exchange abnormalities. Host factors are believed to be important in the pathogenesis of the characteristic inflammation in COPD, as are viruses (Proud and Chung-Wai 2006). Also, host behavior in response to viruses and possible aberrant antiviral host responses may influence the persistence of inflammation following exposure to viruses. In stable COPD latent respiratory viruses, such as RSV or adenoviruses have been associated with accelerated lung function decline, independent of smoking status, exacerbation frequency, and lower airway bacterial load (Mallia and Johnston 2006). RSV may also be associated with systemic inflammation. Whether other viruses, such as different influenza strains, have similar effects in stable COPD is at present unknown. It has been shown that respiratory viruses, such as RSV and also influenza viruses, enter into the bronchial epithelial cells where they can replicate and result in epithelial cell destruc-

tion and necrosis. This results in increased permeability of the mucosa, which allows other pathogens and irritants to penetrate, leads to neurogenic inflammation by substance P and bradykinin, M2- and β 2-receptor dysfunction, and contributes to bronchial hyperresponsiveness (Wilkinson et al 2006). Airway hyperresponsiveness causes excessive airway narrowing in COPD patients.

Viruses are not only involved in the inflammation of stable COPD, but they also can trigger exacerbations (Rohde et al 2003; Wedzicha 2004). Exacerbations are commonly defined as events in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication in patients with underlying COPD (NHLBI 2006).

Respiratory viruses are considered to be amongst the most important triggers of exacerbations. Between 15% and up to 64% of COPD exacerbations have been found to be associated with symptomatic colds precipitated by viruses (Seemungal et al 2001; Wedzicha 2004). Of these, rhinovirus and enteroviruses, both belonging to the picornavirus group of RNA viruses, stand out. Coronavirus, adenovirus, RSV, Influenza A and B, and parainfluenza viruses have been linked with COPD exacerbations and often multiple viruses can be detected (Rohde et al 2003). Various mechanisms are believed to be involved in the way viruses induce or aggravate exacerbations. Rhinoviruses attach to airway epithelium cells through intercellular adhesion molecule-1 (ICAM-1) and thereby cause inflammatory cell recruitment and activation. Also, viral infections were found to be associated with increased oxidant stress, the activation of nuclear factor κ B, and the expression of stress-response genes (Wedzicha 2004).

The proportion of exacerbations related to isolation of influenza virus differs between studies and is probably influenced by the number of COPD patients that receive influenza vaccination (Gorse et al 2006). Influenza infections are cause of excess morbidity and mortality in COPD and may affect the progression of the disease. In older studies and in populations that received no influenza vaccination, the hospitalization rates for acute exacerbations of COPD are substantially higher in the influenza season than in the noninfluenza season (Simonsen et al 2000).

Influenza vaccination in COPD patients

Considering the influence of different respiratory viruses in stable COPD and the important role of viral infections

in exacerbations, vaccination is a potentially effective way to reduce morbidity and mortality caused by exacerbations. Unfortunately, significant variation within the major virus types causing disease limits the success of vaccination programmes. Since influenza viruses display antigenic shift and drift, new vaccines must be developed at regular intervals. In response to the arrival of new pandemic strains, new vaccines must be made available in sufficient quantities. The effectiveness of the vaccines, usually inactivated virus vaccines containing 3 virus strains (2 type A and 1 type B) depends on the similarity between the strains in the vaccine and the virus strains likely to circulate in the upcoming winter. Protection occurs through circulating antibodies to H and N or stimulation of cytotoxic T-cell responses. Protection by influenza vaccination is only effective in 70% of patients and only lasts for one year (WHO 2005). New vaccines must be prepared each year to cover the expected change in antigenicity. As a consequence, by definition supplies are limited in case of an emerging epidemic. Obviously, the benefit of vaccination is largest in epidemic years when the vaccine strain is similar to the epidemic strain.

Currently, all standards and guidelines therefore recommend annual influenza vaccination in all patients with COPD as a cost-effective intervention, in spite of the fact that there are no randomized studies of influenza vaccinations in patients with COPD (NHLBI 2006).

Evidence to support this recommendation largely stems from observational studies in elderly subjects. In a large cohort study of nearly 150,000 elderly patients, vaccination resulted in a reduction of 32% in the numbers of hospitalizations for all respiratory conditions and a reduction of about 50% in all-cause mortality compared with nonvaccinated subjects (Nichol et al 1999). In subjects with chronic lung diseases, vaccination resulted in a 52% reduction in hospitalizations and a 70% decrease in death rates during influenza seasons (Nichol et al 1999). A meta-analysis of published effects of influenza vaccination by Gross and colleagues (1995) showed a 56% reduction in respiratory illnesses, a 50% reduction in hospitalizations, a 68% reduction in all cause deaths, and a 53% reduction in pneumonia in vaccinated subjects. In a randomized clinical trial, Wongsurakiat and colleagues (2004) demonstrated that influenza vaccination is highly effective in the prevention of acute respiratory illness related to influenza virus infection, regardless of severity of COPD, comorbid diseases, age, gender, or smoking status.

From their extensive review of the literature and the limited number of studies specifically performed in COPD patients, published in the format of a Cochrane review, Poole

and colleagues (2006) concluded that administration of an inactivated influenza vaccination has a clinically important and significant effect in reducing exacerbations, caused by influenza, occurring three or more weeks after vaccination, and probably an effect on the total number of exacerbations in COPD patients. In epidemic years, when the proportion of exacerbations caused by influenza is higher, this effect is likely to be greater. Only limited data on the effects of influenza vaccination on number or duration of hospitalizations, mortality, or outcomes in terms of lung function have been reported.

They also concluded that there was no evidence of an increase in early exacerbations (Poole et al 2006). Yet, in the experience of many clinicians, transient increases in symptoms may occur in the weeks after vaccination.

Treatment of influenza in patients with COPD

Chronic obstructive pulmonary disease patients are susceptible to unfavorable outcomes in case of an influenza infection. Vaccination can help prevent exacerbations, pneumonia, and hospitalization in such patients, but the effects are limited to a certain extent by less than ideal immunization rates and antigenic shifts that decrease the effectiveness of the vaccine. Exacerbations that occur as a result of an influenza virus infection should be treated with inhaled bronchodilators, systemic corticosteroids, and antibiotics aimed at suspected bacterial superinfections and low-flow oxygen when appropriate. Other nonspecific measures such as sufficient fluid intake, bed-rest, antipyretic drugs, and/or cool mist humidifiers are recommended as they are in otherwise healthy adults.

Four drugs are currently available for the prophylaxis or treatment of influenza infections: amantadines (amantadine and rimantadine) and N-inhibitors (zanamivir and oseltamivir). The amantadines inhibit viral uncoating inside host cells. They are effective against influenza A only, and the effects are limited because of the emergence of resistant strains. Also, they have several toxic side-effects that further reduce their usefulness (Jefferson et al 2006). N-inhibitors are effective against all N-subtypes and therefore, other than amantadines, they can be used against all strains of influenza. They act by preventing the release of virions from infected host cells. Generally it is recommended not to use N-inhibitors routinely for seasonal influenza and use these drugs only with associated public-health measures in a pandemic situation (Moscona 2005). Furthermore, both drugs have no significant effect on asymptomatic influenza.

Neuraminidase-inhibitors have been tested in various scenarios, but no studies specifically performed in COPD patients are currently available. Published prophylaxis and treatment trials suggest that both zanamivir and oseltamivir are effective in preventing and treating the symptoms and complications of influenza infection but that they do not prevent the infection in itself and will not prevent avoidance of viruses from the nose. The literature regarding the effects of N-inhibitors for preventing and treating influenza in healthy adults has recently been reviewed by Jefferson and colleagues (2006). This excellent review summarizes the result of 52 randomized controlled trials testing N-inhibitors in controlled clinical prophylaxis, post-exposure prophylaxis, and treatment trials. They conclude that oseltamivir in a daily oral dose of 75 mg and of inhaled zanamivir 10 mg daily have no effect in prophylaxis of influenza-like illness compared with placebo. Whether higher doses are more effective is uncertain. The efficacy of oseltamivir compared with placebo, orally administered in a dose of 75 mg daily, against symptomatic influenza is 61%. In a dose of 150 mg daily, the efficacy is 73% (Jefferson et al 2006).

These authors argue against the use of these drugs in routine seasonal influenza control.

In general N-inhibitors have low effectiveness, high efficacy, and appear well-tolerated. The possibility of emerging resistance has been put forward. With oseltamivir, resistance has been reported to be around 0.4% (Zambon and Hayden 2001; Monto et al 2006).

In households, the transmission of seasonal influenza has been shown to be interrupted (Welliver et al 2001).

Neuraminidase inhibitors are recommended for the treatment of at-risk patients who present with influenza-like illness and who can start within 48 hours of the onset of symptoms. Ideally treatment is started earlier, preferably within 12 hours after the onset of symptoms (Aoki et al 2003).

Currently, no controlled studies on the effectiveness and the safety of N-inhibitors specifically for COPD patients or patients with other underlying respiratory disease are available. From observational studies it is concluded that N-inhibitors can be used in addition to influenza vaccination in patients with disorders of the respiratory system including COPD, who are at high-risk of developing influenza related complications (Gorse et al 2006; Williamson and Pegram 2002). Under these conditions they can affect respiratory complications such as pneumonia or bronchitis.

At present no robust data are available to support the use of N-inhibitors in avian influenza (Jefferson et al 2006). Oseltamivir has been used in an uncontrolled setting but data

regarding the effectiveness does not allow for reaching a firm conclusion (Leneva et al 2000).

Unlike the older antiviral drugs, amantadine and rimantadine, N-inhibitors rarely cause central nervous system adverse effects, yet these drugs may have side-effects. Zanamivir has been shown to cause bronchospasm in susceptible patients and should be used with caution in COPD-patients (Freund et al 1999). Patients prescribed zanamivir should have fast-acting bronchodilators available. Other side effects of zanamivir include diarrhea, whereas oseltamivir has been shown to be able to cause nausea, vomiting, and retching (Nicholson et al 2000).

Conclusion

Influenza viruses have been shown to be involved in the pathophysiology of COPD, both in stable disease and in exacerbations. Annual influenza vaccinations are recommended for all patients and have been proven effective in all but a few cases. Vaccination remains the gold standard for the prevention of influenza in at-risk subjects, including patients with chronic diseases such as COPD. Recommended treatment of influenza in COPD patients includes the regular nonspecific measures that are generally believed to be helpful in all patients. When used early, preferably within 12 hours after the onset of symptoms, the N-inhibitors, zanamivir and oseltamivir, are useful adjuncts to vaccination for the management of patients at risk of developing influenza related complications, such as COPD patients. N-inhibitors should not be used in routine seasonal influenza control, not even in patients with COPD. In a serious epidemic or pandemic their use is recommended in conjunction with other public health measures, in COPD patients and others alike.

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