Special Article

Prevention of Pneumococcal Disease in Patients with Chronic Cardiometabolic Diseases

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Abstract

Pneumococcal disease is caused by Pneumococcus (Streptococcus pneumoniae) and includes infections of various severity, not rarely fatal. It is grouped into invasive and non - invasive disease. The first class includes meningitis and bacteremia, while the second one includes otitis media and sinusitis. Pneumococcal pneumonia is considered non – invasive, unless there is concurrent bacteremia in which case it is considered invasive. Severity and invasiveness of the disease depend on the pneumococcal serotype (there are more than 90 different serotypes). Patients at increased risk for pneumococcal disease and especially invasive one are those of advanced age, patients with asplenia, chronic lung disease, diabetes, cardiac disorders, cochlear implants, ESF leak, HIV infection, various immunodeficiencies etc. The prevention of pneumococcal disease is through vaccination. There are two pneumococcal vaccines available to the adult population. The 23-valent polysaccharide vaccine and the latest 13-valent conjugate one. Both are included in the current official recommendations. The conjugate vaccine should be administered first, followed by the polysaccharide one, with an interval of at least 8 weeks. A recent study of the 13-valent conjugate vaccine (CAPITA study) showed that it can reduce the incidence of community-acquired pneumonia and the invasive pneumococcal disease caused by the serotypes included in the vaccine. Despite the documented protection of vaccination against pneumococcal disease, the vaccination coverage of patients with chronic cardiometabolic diseases is far from being sufficient. It is an important task of treating physicians to promote the vaccination coverage of vulnerable patients.

Keywords: Pneumococcal disease; Cardiometabolic diseases; Prevention

Introduction

Pneumococcal disease is caused by Pneumococcus (Streptococcus pneumoniae), a gram-positive, encapsulated diplococcus which initially colonizes the upper respiratory tract and subsequently may cause various infections of varying severity (Westerink, et al., 2012). Pneumococcal disease is classified as invasive, when the bacteria infects normally sterile sites (e.g. meningitis, bacteremia) and non-invasive, when there are mucosal infections (e.g., acute otitis media, sinusitis). The case of pneumonia is special, because it is usually classified as a non-invasive disease, while in case of concurrent bacteremia it is characterized as invasive (Drijkoningen & Rohde 2014). There are more than 90 different serotypes of Pneumococcus and 23 of those are estimated to be responsible for 80-90% of cases of invasive disease (Aliberti, et

al., 2014). The severity of disease caused and the antibiotic resistance depend on the responsible serotype. The prevailing serotypes vary among countries and at different time periods (Aliberti, et al., 2012).

Epidemiology

In a study conducted in 2010, the overall incidence of invasive pneumococcal disease was estimated to be 5.2 cases per 100,000 population, with age extremes having a higher rate (18.5 at 65 years) (Torres, et al., 2015). Pneumococcal pneumonia is bacteremic, therefore invasive, in only 20% of cases, but these cases of bacteremic pneumococcal pneumonia constitute 80-90% of all cases of pneumococcal invasive disease Fedson & Guppy 2013). The magnitude of the problem becomes even more apparent when taking into account that S. pneumoniae is the pathogen most frequently isolated in cases of community-acquired pneumonia, both in those treated in hospital or ICU and those treated in the outpatient setting (Welte, et al., (2012). It is worth noting that the mortality rate of pneumococcal disease remains high despite the developments in antimicrobial chemotherapy, reaching a 10-25% in cases of invasive disease (Lexau, et al., 2005). In 2013, more than 20% of fatal infections of the lower respiratory tract were due to pneumococcal pneumonia (GBD, 2013). This significant mortality rate is due to the fact that community acquired-pneumonia, especially pneumococcal one, in addition to other complications, has been associated with the occurrence of acute cardiac events caused through different mechanisms (Musher, et al., 2007, Corrale-Medina, et al., 2012).

Predisposing Factors

There is a number of conditions (comorbidities) the presence of which increases the risk of pneumococcal disease. The most important conditions are asplenia, CSF leak, cochlear implants, HIV infection, diabetes, chronic heart disease, smoking, chronic liver disease, alcoholism, asthma and chronic lung disease (Shea, et al., 2014). The risk for a patient presenting with a combination of comorbidities is even higher.

Another very important risk factor is age and the risk in patients aged > 65 years can be even nine-fold higher (Shea, et al., 2014). Specifically for diabetes mellitus, the risk for developing pneumonia is increased by 1.4 times and for invasive pneumococcal disease by 1.4 to 6 times (Torres, et al., 2015). Diabetes mellitus has also been found as an independent risk factor for bacteremia in subjects with pneumococcal pneumonia (X1.67 times), which of course is associated with increased mortality rate compared to non bacteremic pneumonia (Torres, et al., 2015).

The increased risk of pneumococcal disease in diabetic patients is due to the damaging effect of hyperglycemia on immune and / or lung function (Torres, et al., 2015). For heart diseases, subjects with congestive heart failure or cardiovascular disease have a three point three -fold increased risk for community-acquired pneumonia, and a nine-fold one for invasive pneumococcal disease (Torres, et al., 2015).

Prevention of Pneumococcal Disease

Pneumococcal disease is a serious condition with significant mortality rates. Patients with chronic cardiometabolic diseases are at increased risk to develop it and especially in a severe form. This makes the prevention of this disease in the above subjects imperative. The need for prevention increases, if we take into consideration that the management of pneumococcal disease is not always an easy task, due to the problem of resistance of Pneumococcus to various antibiotics. Vaccination plays an important role in the prevention of pneumococcal disease.

The four basic principles for the design of a successful vaccine against S. pneumoniae are: (Aliberti, et al., 2012).

1. Covering as many serotypes as possible

2. Covering the most common serotypes

3. Covering serotypes associated with severe disease or antimicrobial resistance

4. Ensuring long-term immunity.

The first vaccine against S. pneumoniae was a whole cell one and it was first used in 1911, followed by polysaccharide vaccines with an increasing number of serotypes. The polysaccharide vaccine (PPSV23) currently in use, is available since 1983 (Torres, et al., 2015). This was followed by the emergence of the so-called pneumococcal conjugate vaccines (originally PCV7, then PCV10 and finally PCV13 in 2011) (Torres, et al., 2015). The appearance of conjugate vaccines is considered a major development. The reason is that, unlike

polysaccharide vaccines, conjugate vaccines involve T-lymphocytes and form memory B-cells (T-cell dependent immunity), which results in a long-term immunity. This property is attributed to the fact that the polysaccharide antigens in conjugate vaccines are bound to a carrier protein (de Roux, et al., 2008)

In a study conducted for PCV13, the vaccine was administered to subjects 60-64 years not previously vaccinated with polysaccharide vaccine. PCV13 compared to PPSV23 seemed to elicit higher functional antibody responses in 8 common serotypes. In another study, subjects aged more than 70 years previously vaccinated with PPSV23 were vaccinated again with PPSV23 or PCV13. It was apparent that after the initial vaccination with PPSV23, the use of PCV13 increased the functional antibody response in 10 common serotypes compared to revaccination with PPSV23 (Jackson et al., 2013a, Jackson et al., 2013b).

CAPITA study recently conducted in a clinical setting (PCV13 vs placebo) assessed the prevention of CAP (communityacquired pneumonia). The study enrolled almost 85.000 subjects aged >65 years (Bonten, et al., 2015). The results were quite interesting, as a statistically significant difference was demonstrated in favor of the vaccine for the first episode of confirmed pneumonia due to a serotype present in the vaccine, for the first episode of non-bacteremic/non-invasive pneumonia due to a vaccine serotype and for the first episode of invasive pneumococcal disease from a vaccine serotype. The final conclusion of the study was that PCV13 protects against pneumococcal, bacteremic and non bacteraemic community-acquired pneumonia and invasive disease caused by serotypes present in the vaccine, but does not protect against all-cause community- acquired pneumonia.

The main characteristics of the two anti-pneumococcal vaccines currently in use are shown below (Pneumo 23R, 2012, Prevenar 13R, 2015).

PPSV23

Indications: Prevention of pneumococcal pneumonia and systemic pneumococcal. infections caused by the serotypes contained in the vaccine, for use in persons aged ≥2 years who are at increased risk.

Adverse Events: Local reactions at the injection site (pain, erythema, induration, swelling). They are mainly mild and transient. Arthus-type reactions have been rarely reported, which are reversible without sequelae (mainly in subjects with high anti - pneumococcal antibody titers).

Systemic reactions: Moderate and transient, fever (2%), rarely >39˚C. It occurs just after the vaccination and resolves in 24 hours. Other general reactions: Lymphadenopathy, rash, urticaria, arthralgia, anaphylactoid reactions, headache, myalgia, malaise, asthenia, fatigue.

PCV13

Indications

i. Children: Active immunization for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to 17 years of age.

ii. Adults: Active immunization for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adult's ≥18 years of age and the elderly.

Common adverse events

i. **Local reactions**: pain, erythema, tenderness, induration

ii. Decreased appetite, headache, diarrhea, vomiting, chills, fatigue, rash, arthralgia, myalgia Both vaccines are included in the Hellenic National Vaccination Program for adults and are recommended for all persons aged 65 years and older, and under conditions in younger people aged 19- 64 years (Ministry of Health & Social Solidarity, 2015) These conditions include anatomical or functional asplenia, chronic respiratory problems, diabetes mellitus, heart diseases etc.

In practice, in order to achieve better protection, both vaccines should be administered, but never concomitantly. Initially PCV13 should be administered, followed by PPSV23 at least 8 weeks apart. If PPSV23 has been used first, PCV13 may follow with an interval of at least 1 year. PCV13 is administered only once. PPSV23 booster dose is given after 5 years, with a maximum number of 3 doses in lifetime. The final dose should be administered after the age of 65 years. Importantly each of the two vaccines can be co-administered with influenza vaccine if

injected at different site (Pneumo 23R, 2012, Prevenar 13R, 2015).

The Issue of Vaccination Coverage

Unfortunately, while scientific data strongly support antipneumococcal vaccination of all vulnerable individuals, the reality is disappointing. The preliminary results of an ongoing survey conducted in the Diabetes Outpatient Clinic of the General Hospital of Attika "KAT" showed that among diabetic patients examined over a 10-month period, only 17% were vaccinated against Pneumococcus. It is worth noting that 60% of patients were aged 65 years and older, which by itself is an indication for this vaccination.

In general, there is a problem on adult vaccinations, which are well-insufficient. The role of the physician is critical for the promotion of vaccination. Based on the results of relevant surveys, the recommendation by the doctor is the most important motivation for the patient to be vaccinated (National Foundation for Infectious Diseases, 2010a, National Foundation for Infectious Diseases 2010b). Doctors must be convinced that the physician who recommends and performs the appropriate vaccinations offers high-quality health care and promotes the safety of the patients and the community.

It was estimated in the late 20th century that the life expectancy of people in the US increased by 30 years compared to the early 20th century. Twenty five out of these 30 years are attributed to 10 advances in the public health. Vaccination is among the first ones of them [22].

In **conclusion**, pneumococcal disease has significant risks for all people, but especially the elderly and those with serious underlying diseases, such as those with chronic cardiometabolic diseases. Although there are effective vaccines that can offer protection, vaccination level of people at risk are very low. It is an important task of treating physicians to promote the vaccination coverage.

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