Recommendations for vaccination against pneumococcus in patients with kidney diseases in Spain

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ABSTRACT

Invasive pneumococcal disease (IPD) is a serious problem in some risk groups: patients with stage 4 and 5 chronic kidney disease, stage 3 CKD undergoing immunosuppressive treatment, nephrotic syndrome or diabetes. These individuals are more susceptible to acquire the infection and are more prone to suffering more severe episodes with worse outcome. Vaccination is one of the strategies for preventing IPD, although vaccination coverage in this group at present is lower than desired. Currently, there are two vaccinations available for adults. The polysaccharide vaccine (PPSV23), used for decades in patients over the age of 2, includes a higher number of serotypes (23), but it does not generate immune memory, causing an immune tolerance phenomenon and it does not act on nasopharyngeal colonization. The conjugate vaccine (VNC13) can be used from infancy until adulthood (advice in patients over 18 years old received approval from the European Medicines Agency in July 2013) and generates a more powerful immune response than PPSV23 against the majority of the 13 serotypes that are included. The 16 scientific societies most directly involved with the groups at risk of IPD have discussed and drafted a series of vaccination recommendations based on scientific evidence related to pneumococcal vaccination in adults with underlying conditions and pathologies, which are the subject of the document "Consensus: Pneumococcal vaccination in adults with underlying pathology". This text sets out the vaccination recommendations for the chronic kidney disease population.

Keywords: Vaccination. Pneumococo. Consensus documents. Chronic kidney disease. Renal transplantation.

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Recomendaciones de vacunación frente a neumococo en enfermos renales en España

RESUMEN

La enfermedad neumocócica invasiva (ENI) supone un grave problema en algunos grupos de riesgo: los pacientes con enfermedad renal crónica estadios 4 y 5 y aquellos con estadio 3 y tratamiento inmunosupresor, síndrome nefrótico o diabetes. Estos individuos son más susceptibles de adquirir la infección y más propensos a padecer cuadros de mayor gravedad y peor evolución. Entre las estrategias para prevenir la ENI se encuentra la vacunación, aunque las coberturas vacunales en este grupo son más bajas de lo deseable hoy en día. Actualmente, disponemos de dos vacunas para el adulto. La vacuna polisacárida (VNP23), que se emplea en mayores de 2 años de edad desde hace décadas, es la que mayor número de serotipos (23) incluye, pero no genera memoria inmunitaria, provoca un fenómeno de tolerancia inmunitaria y no actúa sobre la colonización nasofaríngea. La vacuna conjugada (VNC13) puede emplearse desde lactantes hasta la edad adulta (la indicación en mayores de 18 años ha recibido la aprobación de la Agencia Europea de Medicamentos en julio de 2013) y genera una respuesta inmunitaria más potente que la VNP23 frente a la mayoría de los 13 serotipos en ella incluidos. Las 16 sociedades científicas más directamente relacionadas con los grupos de riesgo para padecer ENI han trabajado en la discusión y elaboración de una serie de recomendaciones vacunales basadas en las evidencias científicas respecto a la vacunación antineumocócica en el adulto con condiciones y patología de base que se recogen en el documento «Consenso: Vacunación antineumocócica en el adulto con patología de base». En el presente texto se recogen las recomendaciones de vacunación para la población de enfermos renales crónicos.

Palabras clave: *Vacunación. Neumococo. Consenso sociedades. Enfermedad renal crónica. Trasplante renal.*

INTRODUCTION

Since June 2010, the conjugate vaccine against 13 *Streptococcus pneumoniae* serotypes is available in Spain,

and its indication for preventing invasive pneumococcal disease (IPD) was extended to adults over 50 years of age by the European Medicines Agency in October 2011[1]. During 2012, several autonomous communities[2-4], as well as some scientific societies[5,6], published their updated recommendations on pneumococcal vaccination in adults by medical indications or because of their pertenence to risk groups, in whom the conjugate vaccine may provide a major benefit.

Lastly, in 2013, 16 scientific Primary Care societies and different specialties prepared the consensus document on pneumococcal vaccination in adults with an underlying disease, which also included recommendations referring to chronic kidney disease (CKD)[1].

In this document, we summarise the recommendations that affect patients with different stages of CKD and different comorbidity factors.

PNEUMOCOCCAL DISEASE: EPIDEMIOLOGY

S. pneumoniae is a major cause of morbidity and mortality in the world, and is responsible for diseases that are preventable with vaccines in which it causes the greatest mortality[7]. According to estimations by the World Health Organization, it is the cause of 1.6 million deaths annually, those most affected being young children and elderly people[8]. In Spain, S. pneumoniae is the most commonly identified pathogenic agent in community-acquired pneumonia (CAP), responsible for up to 63.7% of cases, depending on the series[9]. During the 2003-2007 period, a total of 75 932 deaths were recorded due to CAP in adults of at least 50 years of age[10]. Mortality associated with pneumococcal pneumonia varies between <1% in young adults and 10%-30% in bacterial pneumonia in the elderly[11].

Clinical conditions

IPD is the most severe form of pneumococcal infection and it is defined as the presence of *S. pneumoniae* in blood, cerebrospinal fluid (CSF) or another normally sterile fluid[12]. The highest IPD incident rates occur in the extreme ages of life[13]. According to data of our country (2007-2009), the mean annual incidence rate in children under 2 years of age is 49.79 cases/10^5 inhabitants and 20.76 cases/10^5 inhabitants older than 65 years of age[14].

IPD may occur in different clinical forms, with bacterial pneumonia being the most commonly reported. In adults, 60%-87% of all cases of pneumococcal bacteraemia are attributable to pneumonias[15].

One of the main clinical conditions caused by *S. pneumoniae* is pneumonia, especially CAP. However, the microbiological documentation of pneumonic conditions is not always possible and furthermore, only a small percentage cause bacteraemia, and as such, not all cases may be considered to be IPD. The incidence of CAP in our country in individuals older than 65 years of age is estimated to be 14 cases per 1000 people-year (95% confidence interval 12.7-15.3) and it increases with age (29.4 cases per 1000 people-year in individuals older than 85 years of age)[16]. It is also a major burden, since up to 75% of cases require hospitalisation[17].

Risk factors

As well as age, it has profusely been reported that certain concomitant diseases increase the risk of IPD and its evolution (Table 1). These include medical conditions that lead to a state of immune deficiency, such as chronic kidney, liver, respiratory and cardiovascular diseases, infection by the human immunodeficiency virus (HIV), patients waiting for a solid organ transplantation (and those who have already received an haematopoietic stem cell transplant), patients on chemotherapy due to a solid tumour or malignant haemopathy, those with autoimmune disease treated with corticosteroids, immunosuppressants or biological products, diabetic patients and patients with CSF fistulae, cochlear implants, and functional or anatomic asplenia[10,17,18].

The underlying disease, apart from increasing the risk of IPD, may influence the type of clinical presentation and its subsequent outcome, and therefore, the IPD fatality rate significantly increases in patients with comorbidities that involve immunosuppression (Table 1)[1].

Kidney disease as a risk factor for pneumococcal infection

Acute infections (bacterial, viral and fungal) substantially contribute to high hospitalisation and mortality rates in patients with CKD[19]. There are many factors that predispose CKD patients to infections, which are directly related to different aspects of renal failure.

- The nephrotic syndrome has been related to an increase in the number and severity of infections, due to peripheral oedema, the loss of alternative complement pathway factors and abnormalities in leukocyte and spleen function[20].
- In CKD, malnutrition, the increase in intracellular calcium, iron overload, dialysis membranes and uraemic toxins have been related to abnormalities s in polymorphonuclear function.
- On the setting of acute renal failure, abnormal lymphocyte and monocyte-macrophage function has been reported.

- Increased exposure to pathogens due to an "excessive use of healthcare facilities"[21].

Although there are no studies that directly relate both variables, hospitalisation rates increase significantly as CKD progresses. Due to the foregoing, it seems reasonable to address the issue of a vaccination policy specifically focused on CKD, which on the other hand is a population group in which available vaccines are generally underused.

Therefore, the KDIGO (Kidney Disease Initiative Global Outcomes) guidelines published in 2013 recommend that all adults with CKD stages 4-5 and those on stage 3 with an increased risk (nephrotic syndrome, diabetes mellitus or on treatment with immunosuppressants) (Table 2) receive a pneumococcal vaccine, unless it is specifically contraindicated[21]. We know that the vaccine response in these patients is reduced and that the loss of titres is quicker, which must be taken into account for revaccinations[20].

Table 1. Patients considered to be immunocompromised or immunocompetent with other underlying pathologies or risk factors

Patients considered to be immunosuppressed or immunocompromised	– Hodgkin's disease, leukaemia, lymphoma – Multiple myeloma – Stage 4-5 chronic kidney disease[a] – Stage 3[b] chronic kidney disease with increased risk (nephrotic syndrome, diabetes mellitus or treatment with immunosuppressant drugs) – Solid organ or haematopoietic stem cell transplantation[c] – Chemotherapy or immunosuppression[d] – Human immunodeficiency virus (HIV) infection[e] – Autoimmune inflammatory rheumatic disease[f] – Inflammatory bowel disease (includes Crohn's disease and ulcerative colitis)[g]
Immunocompetent patients with other underlying pathologies or risk factors	– Chronic respiratory disease (includes chronic obstructive pulmonary disease, severe asthma[h] and diffuse interstitial lung disease) – Chronic liver disease (includes cirrhosis) – Chronic cardiovascular disease (includes coronary heart disease, congestive heart failure and stroke) – Diabetes mellitus treated with oral anti-diabetic drugs or dependent on insulin – Smoking[i] – Alcohol abuse[j]

[a] Situation in which the patient maintains an estimated glomerular filtration rate below 30ml/min/1.73m^2. The glomerular filtration rate measurement is based on standardised serum creatinine and the application of the CKD-EPI formula; [b] Situation in which the patient maintains an estimated glomerular filtration rate of 30-59ml/min/1.73m^2; [c] If the patient is on the solid organ transplantation waiting list, vaccinate 2-4 weeks before; if they have already received the transplant, wait 6 months. In haematopoietic stem cell transplantation, vaccination is not recommended before transplantation, but rather 3-6 months after; [d] Vaccination at least 10-14 days before starting treatment (preferably 4-6 weeks) or 3 months after completing chemotherapy or radiotherapy. Those vaccinated during treatment (or 2 weeks before the start of treatment) require revaccination 3 months after it ends; [e] Preferable with a better immune status (in general, above 200 cells CD4/mm^3); [f] Vaccinate during the stable phase of the disease. It can be administered during treatment with anti-tumour necrosis factor, but it is preferable before starting treatment with methotrexate or rituximab or 1-3 months after ending treatment; [g] It is advisable to vaccinate at the time the disease is diagnosed. Vaccination is safe during treatment with immunosuppressive or biological drugs. Thiopurines did not decrease the efficacy of the vaccine. Anti-tumour necrosis factor, methotrexate or a combination of drugs decrease its efficacy, and as such, it is preferable to vaccinate before starting using these drugs; [h] High-risk asthmatic patients (one or more hospitalisations or visits to the emergency department; use of oral corticosteroids); iIncludes active smokers with a load of 15 or more years/packet without comorbidity; ex-smokers with a load of at least 20 years/packet and who have not smoked for at least 10 years; and any smoker regardless of their age, and intensity and/or load, who suffers from a respiratory disease; jincludes people with a drinking problem and alcohol dependence syndrome: in males, more than 28 SU/week and in females more than 17 SU/week (SU: standard unit, which is equivalent to 10 grams of pure alcohol present in a glass of wine [100cm^3] or a small beer, for example).

Table 2. Vaccination recommendations in adults with an underlying disease

	Not previously vaccinated	Previously vaccinated with PPV23 (≥1 year)
Immunocompromised[b,c] CSF fistulas Cochlear Implants Functional or anatomic asplenia	PCV13 → PPV23 (minimum interval 8 weeks)	PCV13 Booster with PPV23 if ≥5 years from the first dose[a]
Immunocompetent with another underlying pathology	PCV13	PCV13
Renal transplantation waiting list	PCV13 on the waiting list 2-4 weeks before transplantation. If patient has already received a transplant, he must wait 6 months	PCV13 with the same time references as those not vaccinated

[a] Revaccination with a second dose of PPSV23, with a minimum interval of 8 weeks after PCV13, if it has been more than five years since the administration of the first dose of PPSV23, up to a maximum of two doses; [b] Patients undergoing haematopoietic stem cell transplantation, according to the recommendations of international consensus, should receive three doses of vaccine PCV13 (from 3 months after transplantation) with a minimum interval of one month between doses and one dose of PPSV23 8 weeks after the last dose of PCV13, whenever 12 months have elapsed since transplantation. If there is graft-versus-chronic host disease, we recommend replacing this polysaccharide vaccine booster dose with a conjugate vaccine; [c] Patients being treated with methotrexate or rituximab may require two doses of PCV13 vaccine or wait 1-3 months after treatment has ended.

PNEUMOCOCCAL VACCINE

23-valent pneumococcal polysaccharide vaccine

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) was included in the adult vaccination schedule in Spain between the years 2003 and 2005, depending of the different autonomous communities.People older than 60 years of age vaccinated more than five years before due to any of the above mentioned indications before this age[22]. The recommended regimen is one dose to individuals 60 year-old or older and to individuals over 2 years of age who had a risk factor (Table 1), such as: chronic diseases (cardiovascular, pulmonary [except asthma] or metabolic diseases), functional or anatomic asplenia, chronic renal failure, liver cirrhosis, diabetes mellitus, alcoholism, CSF fistulae, cochlear implants, infection due to HIV, immunosuppressive diseases and chemotherapy[23].

One sole revaccination (second dose) is currently recommended to those who were vaccinated more than five years before and fulfilling the following criteria:

- People older than 60 years of age vaccinated over five years before due to any of the foregoing indications before this age.
- Individuals of any age with a high risk of severe pneumococcal disease in cases such as asplenia, chronic renal failure, nephrotic syndrome or any other immunosuppression[22].

PPSV23 induces an independent immune response from T cells in 80% of healthy adults, although with a different magnitude according to the serotypes included in the vaccine, as well as age and the comorbidity of the patient being vaccinated[22]. PPSV23 efficacy based on observational studies, shows in a meta-analysis an efficacy in healthy immunocompetent adults of 50%-80% in the prevention of invasive disease, without a conclusive demonstration of protection against non-bacterial pneumonia[24]. However, the analyses of the efficacy of this vaccine in risk groups have not demonstrated significant protection against infection by pneumococcus, with low serological response rates, which did not improve after the administration of the second vaccine dose[25].

Furthermore, this vaccine has other disadvantages:

- Antibody titers progressively decrease after vaccination, until they reach pre-vaccine levels after a period of 3 to 10 years[26].
- Absence of immunological memory or anamnestic response with poor memory B lymphocyte recruitment[27].
- Induction of the immune tolerance or hyporesponsiveness phenomenon with revaccinations[28]. The immune response

to revaccinations compared to most serotypes is lower than that observed after the primary vaccination. As such, the second dose of the vaccine is not considered to be a booster.

- It does not act on nasopharyngeal colonisation, a key factor in the epidemiology of pneumococcal infections and, as such, it does not provide significant protection against pneumococcal infections of the mucosa or against the decrease in antibiotic-resistant pneumococcal strains[29].

Conjugate pneumococcal vaccine

PCV13 is a conjugate pneumococcal vaccine that provides protection against 13 *S. pneumoniae serotypes*[1]. The 13 pneumococcal serotypes included in this vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) are responsible for at least 50%-76 %[18] of cases of IPD in adults of 50 years of age or older[2].

PCV13 received authorisation to be marketed in Europe for use in infants and young children in December 2009 and it has been available in Spain since June 2010[2]. The impact of its use in our country is observed in a 55% reduction in the hospitalisation incidence rate due to IPD ($p<.001$) in children younger than 15 years of age, which increases to 63% ($p<.001$) in those between 12 and 24 months[30].

Furthermore, this vaccine has the advantage of sensitising the immune system so that it may create a booster response to a second administration of either of the two vaccines, and therefore, the conjugate vaccine induces immunological memory[31].

VACCINATION/FINANCING GUIDELINES/ RECOMMENDATIONS

The current vaccination guidelines and the type of vaccine that must be used in the different risk groups are specified in Table 2.

On 17 July 2012, the Directorate General of the National Health and Pharmacy System's Basic Services Portfolio decided to include in the National Health Service's pharmaceutical services, using public funds, the indication of active immunisation for the prevention of IPD caused by *S. pneumoniae* in **adults of 50 years of age** or older, with the following indications: immunosuppressive treatments, Hodgkin's disease, leukaemia, lymphoma, multiple myeloma, renal failure, nephrotic syndrome, solid organ or haematopoietic stem cell transplantation, chemotherapy and infection due to HIV.

Following the recent positive evaluation by the Committee for Medicinal Products for Human Use of the European Medicines Agency for the extension of the indication to

KEY CONCEPTS

1. IPD is an important cause of morbidity and mortality in the world.
2. Comorbidity is a risk factor for incidence and poor prognosis.
3. Vaccination reduces infections and antibiotic resistance (demonstrated in the child vaccination).
4. The PPSV23 vaccine is complete, but it does not generate an immunological memory. It does not reduce risk.
5. The PCV13 vaccine is useful from the first 6 weeks of life, it is more powerful and it generates memory.
6. A clear benefit is expected from applying this consensus.
7. Most cost-effective measure: vaccinating children (indirect protection on reducing overall incidence). If not, vaccinate adults at risk.
8. Immunosuppressed risk groups: CKD patients stages 4-5 or stage 3 with nephrotic syndrome, diabetes or immunosuppressive treatment, patients with renal transplant and other pathologies.
9. Non-immunosuppressed risk groups: chronic obstructive pulmonary disease, liver disease, diabetes and cardiovascular disease.
10. Objective: vaccinate adults of groups 8 and 9 with at least one dose of PCV13; those who require a PPSV23 booster must first undergo the administration a dose of PCV13.

adults older than 18 years of age, it is likely that in a short period of time the National Health and Pharmacy System will also modify this service. In turn, some autonomous communities have extended the aforementioned indications and the age range.

There is currently no public financing for some recommendations carried out in this consensus document (Table 2), and as such, prescription must be done indicating to the users that they must pay the full price. Additionally, we should bear in mind that the 2013 KDIGO guidelines recommend revaccinations every five years for all patients with CKD who have already been vaccinated, unless this is contraindicated[22].

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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