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Pneumococcal disease: current challenges in patients with chronic kidney disease and diabetes mellitus

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Abstract: Pneumococcal disease is defined as any infection caused by the bacteria Streptococcus pneumoniae; it is called invasive when the isolation of this microorganism is confirmed in sites of the body that are normally sterile, such as blood and cerebrospinal fluid, and non-invasive when the infection occurs in sites of the body that are normally non-sterile. Chronic kidney disease and diabetes mellitus are important risk factors for the development of pneumococcal disease due to their status of immunosuppression; therefore, anti-pneumococcal vaccination is a fundamental preventive measure in patients who suffer from these conditions.

Key words: chronic kidney disease; mellitus diabetes; streptococcal infections

1 Pneumococcal disease

Pneumococcal disease (PD), also known as pneumococcal infection, is defined as any infection caused by the gram-positive coccus microorganism Streptococcus pneumoniae, also called pneumococcus [1,2]. Infections caused by this microorganism represent one of the leading causes of morbidity and mortality worldwide [3,4].

PD can be grouped into two main categories: invasive and non-invasive [5]. The latter is where the infection occurs in body sites that are not normally sterile: sinusitis, acute otitis media and community-acquired non-bacteremic pneumonia (CAP) [1] (Figure 1).

Streptococcus pneumoniae is responsible for more than 25% of bacterial pneumonias, with this pulmonary infection being the main presentation of non-invasive pneumococcal disease [1]. The incidence of community-acquired pneumonia (CAP) varies worldwide, ranging from approximately 1.6 to 11.6 cases per 1,000 people in Europe [5]; in the United States, it was established that 266.8 cases per 100,000 people with CAP required hospitalization [6]. However, these latter figures

have decreased following the introduction of the pneumococcal vaccine, reaching 54.8 cases per 100,000 people per year [7,8].

In turn, invasive pneumococcal disease (PD) is defined as an infection confirmed by the isolation of pneumococcus from normally sterile body sites, such as blood and cerebrospinal fluid (CSF) [1]. As such, invasive PD includes bacteremic pneumococcal pneumonia, primary pneumococcal bacteremia without a focus, and pneumococcal meningitis (Figure 1) [5].

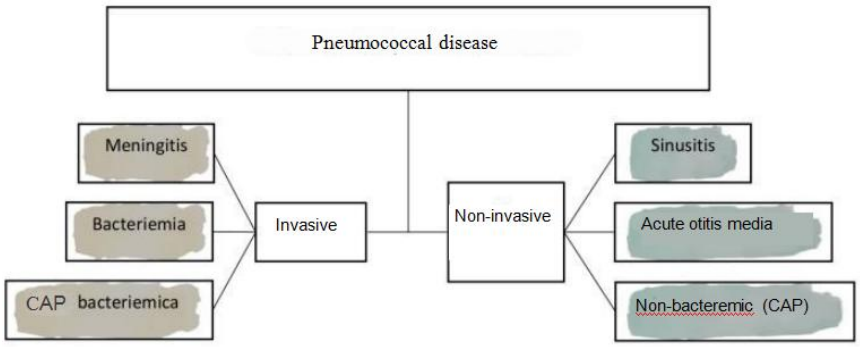

Figure 1. Classification of pneumococcal disease (CAP: community-acquired pneumonia.)

Pneumonia has been described as the most common clinical presentation of invasive pneumococcal disease (PD), accounting for approximately 53% of cases; similarly, primary pneumococcal bacteremia without a focus has been reported in around 40% of cases, and meningitis in 5% [5]. The incidence of invasive PD has been shown to be strongly associated with age, with the highest incidence rates observed in children under 2 years of age and in adults over 65 years of age [9,10]. Immunocompromised patients are at a much higher risk of developing invasive PD [1].

The main risk factors for invasive pneumococcal disease (Figure 2) include older adults, patients with chronic diseases (cardiovascular disease, chronic lung disease, chronic kidney disease (CKD), and uncontrolled diabetes mellitus), smokers, splenectomized patients, immunosuppressed individuals, and those with hematologic malignancies [11–16]. Other described risk factors include cerebrospinal fluid fistula and cochlear implant users [17–20].

2 Pneumococcal disease (PD), chronic kidney disease (CKD), and diabetes mellitus

Patients with chronic kidney disease (CKD) experience impaired innate and adaptive immune response, predisposing them to infections [1]. They also exhibit chronic retention of nitrogenous compounds and cytokines, substances normally eliminated by the kidneys. This condition leads to decreased immune function, evidenced by reduced bactericidal capacity of neutrophils and hyperreactive monocytes, and subsequently decreased differentiation of dendritic cells; decreased production of thymic T cells; impaired activation of T cell responses; decreased B lymphocytes; and activation of T- and B-cell-induced apoptosis [21]. In fact, infectious complications are described as the second leading cause of hospitalization in CKD patients, second only to cardiovascular complications [22, 25].

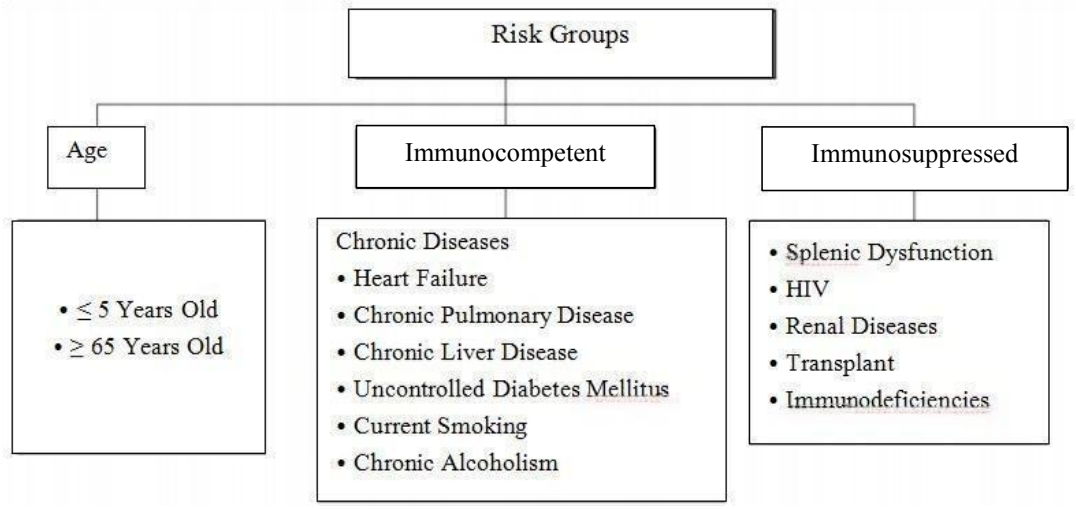

Figure 2. Main risk factors for invasive pneumococcal disease

The term diabetic kidney disease (DKD) refers to functional renal damage induced by diabetes mellitus, which is currently the leading cause of chronic kidney disease (CKD), as it accounts for up to 40% of cases [26].

Approximately 30% of diabetic patients develop CKD at some point in their lives [27, 31]. These patients are at high risk because both conditions (diabetes and CKD) are described risk factors for the development of infectious diseases due to a state of immunosuppression [32, 33].

Community-acquired pneumonia (CAP) is the second most common cause of infection in patients with chronic kidney disease (CKD) and diabetes, especially in those with end-stage CKD; this has been associated with increased mortality and a poor long-term prognosis [34], with pneumococcus being the most frequently isolated bacterial microorganism [35].

Slinin et al. [36] reported a pneumonia hospitalization rate of 84.4 hospitalizations per 1,000 patients per year in a sample of 14,859 hemodialysis patients. That study also established that pneumococcus was responsible for approximately 53% of reported pneumonia cases in dialysis patients [36], while Bonnave et al. [11] reported that the incidence of pneumonia in kidney transplant recipients was approximately 2.62 cases per 100 patients per year. The mortality rate for dialysis patients following an episode of pneumonia is elevated, with data showing rates up to 16 times higher compared to the general population [37,38].

The 6-month mortality rate following an episode of pneumonia in patients in their first year of dialysis therapy was 78.3 per 100 patients per year in 2001. The risk of death in these patients, compared to those on dialysis who did not experience pneumonia, was significantly higher and remained elevated for up to 48 months after the event. Furthermore, dialysis patients with pneumonia had an increased risk of developing cardiovascular events in the first 6 months compared to those without pneumonia [37].

3 Pneumococcal vaccination in CKD

Pneumococcal vaccination is one of the preventive measures that should be used to reduce the risk of developing a pneumococcal disease [39, 40]. Currently, there are two vaccines against this microorganism: the 13-valent pneumococcal conjugate vaccine (PCV13 or Prevenar 13) [41], which contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and the 23-valent pneumococcal capsular polysaccharide vaccine (PPSV23 or Pneumovax 23) [42], which contains serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.

In 2011, a retrospective study was published on 118,533 patients with CKD who were managed with hemodialysis and found that pneumococcal vaccination was associated with a statistically significant decrease in the risk of mortality,

mortality from cardiovascular causes and hospitalization for bacteremia, highlighting the small but significant association between pneumococcal vaccination and decrease in the risk of mortality [43].

However, a diminished response to pneumococcal immunization has been observed in patients with chronic kidney disease (CKD) or on dialysis. For example, a study published in 2009 evaluated the antibody response to the PPSV23 pneumococcal vaccine in CKD patients compared to previously healthy individuals. Blood samples were taken before vaccination and four weeks later, and specific antibodies against whole pneumococcal antigens were measured using the ELISA technique. The study found that after vaccination, 21% of CKD patients exhibited a hyporesponsive response to the immunization and experienced more episodes of pneumococcal infections. In turn, the increase in the proportion of pneumococcal IgG titers in the CKD group was significantly lower compared to the healthy patient group, thus concluding that, although most CKD patients responded adequately to the PPSV23 vaccine, a substantial number did not achieve an adequate antibody response [44].

On the other hand, in 2016 a study was published in which the immunogenicity of the PCV13 vaccine was evaluated in patients with end-stage CKD and under dialysis therapy management and a significant decrease in antibody concentrations for most PCV13 serotypes was found at 12 months of vaccination, in addition the overall response rate to individual serotypes was also low in that same period [45].

Although the overall effectiveness of pneumococcal vaccination in the CKD population is not fully defined, immunization is strongly recommended due to the high mortality associated with invasive pneumococcal disease and the low risk of adverse reactions caused by vaccines [34,46–48].

Pneumococcal immunization is recommended in patients with chronic kidney disease not dependent on renal replacement therapy, in those with nephrotic syndrome, in those requiring immunosuppression, and in diabetics [34]. Similarly, the KDIGO (Kidney Disease Improving Global Outcomes) guidelines [49] recommended pneumococcal vaccination in all patients with a glomerular filtration rate <30 mL/min/1.73 m^2, as summarized in Table 1.

Current recommendations regarding the pneumococcal immunization schedule in patients with CKD vary depending on the patient's characteristics; whether or not they have received previous doses of PPSV23 or PCV13, or whether, on the contrary, they have not received any immunization [50]. In patients under 65 years of age, a conjugate schedule of PPSV23 plus PCV13 is suggested, while in patients older than this age, only the polysaccharide vaccine should be administered.

Table 1. Recommendations from different consensus statements for pneumococcal immunization in patients with chronic kidney disease

Guide	Recommendation
KDIGO-ERC 2012	1. It is recommended that all adults with eGFR <30ml/min/1.73m^2 (Categories G4-G5) and those at high risk of pneumococcal infection (e.g., nephrotic syndrome, diabetes, or those receiving immunosuppressants) receive the polyvalent pneumococcal vaccine unless contraindicated. 2. It is recommended that all adults with CKD who have received pneumococcal vaccination be offered revaccination within 5 years.
ACIP 2019	1. The PCV13 vaccine is not recommended for indiscriminate use by all adults over 65 years of age. 2. The use of the PCV23 vaccine is recommended. 3. It is recommended to select at-risk patients for PCV13 use.

Source: Prepared based on a document from CKD Evaluation and Management [49].

For patients who have previously received immunization with the PPSV23 vaccine, recommendations dictate waiting

at least 1 year after this immunization to administer a dose of the PCV13 vaccine (Table 2) [50].

Table 2. Recommendations of the Advisory Committee on Vaccination Practices for pneumococcal immunization in patients with chronic kidney disease

Recommendations in adults based on risk (ACIP-CDC)			
	Initial Dose	Second Dose	Third Dose
Subjects who do not receive PPV23 prior	PCV13	PPV23 within 8 weeks	
Subjects who received PPV23 prior	previous PPV23	PCV13 at 12 months or later	PPV23 within 8 weeks*

*Immunosuppressed patients: with congenital or acquired immunodeficiencies, HIV infection, chronic kidney disease or nephrotic syndrome, leukemias, lymphomas, disseminated tumors, immunosuppressant drugs, solid organ transplant or multiple myeloma.

Source: Prepared based on a document from CKD Evaluation and Management [49].

For patients who have not previously received pneumococcal immunization and are over 19 years of age at the time of receiving the diagnosis of CKD, it is recommended to administer a dose of the PCV13 vaccine and wait at least 8 weeks before administering the first dose of the PPSV23 vaccine, after which at least 5 years should be allowed before administering the second dose of the latter vaccine (Table 2) [50].

In patients over 65 years of age, a final dose of the PPSV23 vaccine should be administered at least 5 years after the most recent dose of PPSV23 [50].

Similarly, in kidney transplant recipients, immunization with the current vaccines (PCV13 and PPSV23) is recommended according to the previously described schedules; in addition, the pneumococcal conjugate vaccine dose should be repeated when the patient reaches 65 years of age. For this population, not only should individual immunization be considered, but also that of their entire close circle: healthcare workers who are in contact with the patient, close personal contacts, and even pets, all in order to reduce the risk of disease transmission to the transplant recipient [34].

4 Conclusion

Chronic kidney disease (CKD) and diabetes mellitus are significant risk factors for the development of infectious diseases such as pneumococcal disease. Vaccination is the most effective preventive measure worldwide to avoid infectious complications; therefore, physicians treating patients with these two conditions should prioritize administering the recommended pneumococcal vaccination schedules.

Conflicts of interest

The author declares no conflicts of interest regarding the publication of this paper.

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