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Current Recommendations and Problems of Pneumococcal Vaccination for Patients with Chronic Renal Failure: A Review Article

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Introduction

Pneumonia is a common and serious infectious disease. Patients treated with dialysis have higher pulmonary infectious mortality rates than the general population. *Streptococcus pneumoniae* (*S. pneumoniae*) is the most frequent cause of community-acquired pneumonia in adults, and more than half of the cases of pathogen-causing pneumonia among dialysis patients are reported to be due to *S. pneumoniae*. *S. pneumoniae* also causes invasive infections such as meningitis, bacteremia, or bacteremic pneumonia and is therefore considered a serious threat to public health. For these reasons, pneumococcal vaccines have been developed since the 1970s, and two types of pneumococcal vaccines are currently available for clinical use: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). The 2019 Advisory Committee on Immunization Practices (ACIP) guidelines recommended PCV13 and PPSV23 vaccination for immunocompromised persons aged ≥ 19 years, including those with chronic renal failure (CRF) [1]. Furthermore, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines specifically recommended pneumococcal vaccination among all adults with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² (GFR categories G4 and G5) and those at high risk of pneumococcal infection (e.g., persons with nephrotic syndrome, diabetes, or those receiving immunosuppression) [2]; however, there are few reports supporting this recommendation. Further, the recommendations also refer to lower levels of antibody titer and more rapid loss of antibody titers in renal failure patients as compared to healthy control patients after pneumococcal vaccination. This confusing suggestion was caused by an ambivalent effect of vaccination against infection, namely, immunocompromised persons having a higher incidence of infection while having a lower efficacy of vaccination.

23-Valent Pneumococcal Polysaccharide Vaccine

PPSV23 has been globally approved and used for the prevention of pneumococcal infection in immunocompetent adults and immunosuppressed patients; however, the benefits of PPSV23 vaccination were not clearly showed against all pneumococcal infections and for all target persons. Jackson et al. described the outcomes for ≥ 65 years aged persons after the receipt of PPSV23 in Washington State [3]. 47,365 senior adults were enrolled in the most large-scale retrospective cohort study, and assessed over a three-year period. The association between pneumococcal vaccination and the risk of each outcome was evaluated through multivariate statistical analysis, using 1,428 cohort members who were hospitalized with community-acquired pneumonia, 3,061 who were assigned a diagnosis of outpatient pneumonia, and 61 who had pneumococcal bacteremia. Receipt of PPSV23 was associated with a significant reduction in the risk of pneumococcal bacteremia (hazard ratio (HR), 0.56; 95% confidence interval (CI), 0.33 to 0.93) but a slightly increased risk of hospitalization for pneumonia (HR, 1.14; 95% CI, 1.02 to 1.28). Furthermore, invasive pneumococcal disease (IPD) in an immunocompromised host was not prevented through PPSV23 treatment (HR, 0.78; 95% CI, 0.32 to 1.87). Moberley et al. revealed a Cochrane review evaluating the efficacy of pneumococcal polysaccharide vaccines [4]. For this meta-analysis, twenty-five studies met the inclusion criteria (18 randomized controlled trials (RCTs) involving 64,852 participants and seven non-RCTs involving 62,294 participants). Pneumococcal polysaccharide vaccination was strongly associated with low incidence of IPD (odds ratio (OR), 0.26; 95% CI, 0.14 to 0.45). There was efficacy against all-cause pneumonia in low-income (OR, 0.54; 95% CI, 0.43 to 0.67) but not high-income countries in either the general population (OR, 0.71; 95% CI, 0.45 to 1.12) or in adults with chronic illness (OR, 0.93; 95% CI, 0.73 to 1.19). Furthermore, many clinical trials targeting immunocompromised patients failed to verify the efficacy of PPSV23. Even at this time, the only established efficacy of PPSV23 is the protection against IPDs in immunocompetent adults.

Several reports suggested that PPSV23 prevented the incidence of cardiovascular events. Hung et al. conducted a prospective cohort study of patients aged ≥ 65 years in Hong Kong with ≥ 1 of the chronic illness: asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, hypertension, diabetes mellitus, stroke, chronic renal or liver disease, or malignancy [5]. Out of the 36,636 persons enrolled, 7,292 received both PPSV23 and influenza vaccine, 2,076 received influenza vaccine alone, 1,875 received PPSV23 alone, and 25,393 were unvaccinated, with a duration of follow-up of 45,834 person-years. Dual vaccination was associated with fewer deaths (HR, 0.65; 95% CI, 0.55 to 0.77) and fewer cases of pneumonia (HR, 0.57; 95% CI, 0.51 to 0.64), ischemic stroke (HR, 0.67; 95% CI, 0.54-0.83), and acute myocardial infarction (HR, 0.52; 95% CI, 0.38 to 0.71), compared with unvaccinated groups. Dual vaccination also resulted in fewer coronary (HR, 0.59; 95% CI, 0.44 to 0.79) and intensive care admissions (HR, 0.45; 95% CI, 0.22-0.94), compared with unvaccinated groups. Ren et al. described a systematic review concerning the effect of pneumococcal polysaccharide vaccines on cardiovascular disease [6]. A total of 230,426 patients were included in eight observational studies and recorded as acute coronary syndrome (ACS) events. The receipt of PPSV23 was associated with significantly lower odds of ACS events in patients ≥ 65 years (OR, 0.83; 95% CI, 0.71 to 0.97). Ihara et al described a retrospective cohort study targeted dialysis patients [7]. The medical records of all dialysis patients attending their 8 study centers in 2010 were studied and a total of 510 patients were identified for outcome analysis. The all-cause death rate was significantly decreased in the PPSV23-vaccinated group, (HR, 0.62; 95% CI, 0.46 to 0.83). The hospitalization rate and death rate due to cardiac events were significantly lower in the PPSV23-vaccinated group than in the non-vaccinated group (HR, 0.44; 95% CI, 0.20 to 0.96 and HR, 0.36; 95% CI, 0.18 to 0.71, respectively). Furthermore, several basic researches suggested that the pneumococcal polysaccharide vaccine might directly suppress the progression of atherosclerosis. Binder et al. revealed an *in vivo* study evaluating association between pneumococcal infection and the progression of atherosclerosis [8]. Ldlr-/- mice that received pneumococcal immunization showed high circulating levels of oxidized low-density lipoprotein (oxLDL)-specific immunoglobulin M (IgM) which were related to reducing the progression of atherosclerosis, and the mice decreased the extent of atherosclerosis. It was speculated that an immunological cross-reaction between phosphorylcholine antigens on the cell wall polysaccharide (CWPS) of *S. pneumoniae* and oxLDL occurred. For these reasons, the preventive effects of PPSV23 against pneumococcal infection in patients with CRF were unclear, whereas there was strong evidence that the receipt of PPSV23 may reduce the incidence of cardiac events, resulting in a prolonged prognosis for dialysis patients.

13-Valent Pneumococcal Conjugate Vaccine

The clinical effectiveness and immunization response of PCV13 differ greatly from those of PPSV23. PPSV23 induces

antibodies by T-cell independent humoral immune responses, resulting in a short lived and non-anamnestic response. In contrast, PCV13 induces a T-cell dependent immune response followed by the formation of memory B-cells, so the immune response is generally stronger than that of PPSV23. In pneumococcal conjugate vaccines, the 7-valent pneumococcal conjugate vaccine (PCV7) was first clinically used as mainly childhood immunization, and then it was replaced with PCV13 in most immunization programs. The efficacy of PCV13 in immunocompetent senior adults has had a great impact because PCV13 can prevent not only the incidence of IPD but also pneumococcal pneumonia with or without bacteremia. Bonten et al. conducted a randomized, double-blind, placebo-controlled trial targeting ≥ 65 years aged immunocompetent adults [9]. A total of 84,496 individuals were enrolled in this study. In the per-protocol analysis of first episodes of infections due to vaccine-type strains, community-acquired pneumonia occurred in 49 persons in the PCV13 group and 90 persons in the placebo group (vaccine efficacy (VE), 45.6%; 95.2% CI, 21.8 to 62.5), nonbacteremic and noninvasive community-acquired pneumonia occurred in 33 persons in the PCV13 group and 60 persons in the placebo group (VE, 45.0%; 95.2% CI, 14.2 to 65.3), and IPD occurred in 7 persons in the PCV13 group and 28 persons in the placebo group (VE, 75.0%; 95% CI, 41.4 to 90.8). However, the evidence in immunosuppressed patients including CRF was limited; there were only several reports evaluating immunogenicity. Glesby et al. conducted a prospective study targeting HIV-infected persons in the United States [10]. The study population was previously vaccinated with ≥ 1 dose of PPSV23 and had CD4 cell counts ≥ 200 cells/mm³ and HIV viral loads $<50,000$ copies/mL. Increases in anticapsular polysaccharide IgG concentrations and opsonophagocytic antibody titers were observed. Mitra et al. evaluated immunogenicity in 25 end stage renal disease (ESRD) patients on dialysis, aged ≥ 50 years, who had previously received ≥ 1 dose of PPSV23 [11]. IgG levels of vaccine type were recorded at 2 and 12 months after the receipt of PCV13. Statistically significant increases in geometric mean antibody concentrations (GMCs) were observed for all serotypes at two months; however, the GMCs at 12 months declined by 38% to 72% compared to those measured at 2 months post-vaccination. The effectiveness of PCV13 in CRF was still unclear, because of a lack of clinical data targeting immunosuppressed patients and rapid decline of IgG levels.

Conclusion

ACIP recommended a dual pneumococcal vaccination program in immunocompromised patients: PPSV23 administration ≥ 8 weeks after PCV13 administration, because the dual vaccination suggested a synergized immunogenic effect. Although there were not sufficient clinical data targeting immunosuppressed patients with CRF, dual pneumococcal vaccination is speculated to be the most effective treatment in terms of benefits received from each of the pneumococcal vaccines. The effect of PCV13 against pneumococcal infection may be stronger than that of PPSV23; however, there were not enough clinical data for immunosuppressed patients. Most reports revealed that receipt of PPSV23 was associated with a

reduction of the incidence of atherosclerotic disease, and several basic researches supported the clinical data, namely, that PPSV23 might directly reduce oxidized LDL. Further, these effects have not been yet reported for PCV13. The receipt of PPSV23 was considered as the effective option in dialysis patients for preventing atherosclerotic disease, because CRF patients were at extreme risk of developing atherosclerotic disease, such as acute coronary syndrome, cerebral infarction, and peripheral vascular disorder.

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Conflict of Interest

None declared.

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