Influenza and Pneumococcal Vaccination in Chronic Respiratory Patients – Are We in the Right Path?

Vacunación contra la gripe y el neumococo en pacientes con enfermedad respiratoria crónica - ¿estamos en el buen camino?

Dear Editor:

Chronic respiratory patients (CRP) are either more susceptible to develop infections, or at increased risk of serious complications, hospitalization, long term use of drugs to treat infection, and death.

Vaccination is still the best preventing method to reduce the burden of lower respiratory tract infections, especially pneumonia, in this set of patients. Recommendations by the World Health Organization (WHO) for Influenza vaccination (IV) include CRP, regardless of the age.[1] For pneumococcal vaccination (PV), WHO position statement prioritizes high coverage of infants; the benefits in adults are highlighted, and studies have shown that the 13-valent conjugate vaccine (PCV13) vaccination in the elderly can induce an immune response against vaccine serotypes that is as good as or better than 23-valent polysaccharide vaccine (PPV23). PCV13 is safe and effective in preventing non-invasive and invasive pneumococcal pneumonia.[2–4]

Each country adapts these recommendations based on local epidemiological trends and social and financial circumstances. In our clinical scenario IV is recommended for CRP with asthma under inhaled or systemic corticotherapy, chronic obstructive lung disease (COPD), cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia with a cost ranging from 5.84 to 6.05 EUR (with 37% reimbursement upon medical prescription). However, it is only provided by the national health service for those with cystic fibrosis, alpha-1 antitrypsin deficiency under replacement therapy, interstitial lung disease (ILD) under immunosuppressive therapy, neuromuscular diseases, and for all inhabitants aged 65 or above. Also in our clinical context PV has an average cost of 59.11 EUR (also with 37% reimbursement) and is recommended for those with chronic respiratory insufficiency, COPD, emphysema, asthma under chronic inhaled or systemic corticotherapy, bronchiectasis, ILD, cystic fibrosis, pneumoconiosis, neuromuscular diseases, pulmonary arterial hypertension, active neoplastic disease, transplant receptor or in the waiting list, and under immunosuppression.

The aim of our study was to ascertain the level of IV and PV coverage and its determinants, as well as to identify the main reasons behind adherence to vaccination. To do so, we conducted a cross-sectional study based of the fulfillment of a questionnaire distributed to all CRP that attended our pulmonary outpatient clinic during nearly 5 months (including the influenza vaccine season).

Of the total of 1362 patients that attended our clinic in the study period, 201 patients (14.75%) answered the questionnaire: 59.7% were men, with mean age of 65.3 years (SD = 15.3); 8% were current and 36% former smokers; 81.8% had low vs. 13.1% with medium and 5.1% with high educational status. Major diagnosis registered were asthma (31.3%) followed by COPD (28.9%), ILD (23.4%) and lung cancer (1.0%). The overall coverage for IV and PV was 83.5% and 41.9%, respectively. For IV, 65.9% were vaccinated that present season, 63.5% in the previous one and 53.9% in any other season; 60.4% had had been vaccinated in the last two seasons. Among patients who received PV, 75.6% have been vaccinated with PCV13 and 35.4% with PPV23. Motivation towards vaccination was mainly due to previous medical recommendation (96.6% for IV and 96.1% for PV), followed by communication media (3.4% for IV and 3.9% for PV) and relatives' counseling (1.4% and 0.8% for IV and PV, respectively). The chief hindrances towards vaccination were risk concerns (54.3%) and the possibility of acquiring flu regardless of vaccination (28.6%) for IV; economical concerns (39.3%), followed by risk concerns (25.0%), fear of injections/needles (8.9%) and difficult access to health care (5.4%) for PV. Vaccination rates according to determinants in CRP are showed in Table 1.

Table 1
Vaccination rates (%).

	Influenza vaccination (IV)	Pneumococcal vaccination (PV)
Total (n = 201)	83.5	41.9
Sex		
Male	59.3	61.4
Female	40.7	38.6
Age group		
<40	5.4	4.8
40–74	64.1	65.1
≥75	30.5	30.1
Smoking history		
Smoker	4.9	3.7
Former smoker	34.1	39.5
Non-smoker	61.0	56.8
Educational status		
Low	84.3	81.7
Medium	11.4	13.4
High	4.2	4.9

Using a multivariable binary logistic regression model with forward elimination method, IV coverage was independently associated with age ($p < 0.006$): patients aged ≥75 or 40–75 years were more likely to have IV coverage than patients aged <40 years (OR = 9.28; 95%CI, 2.09–41.26; $p = 0.003$ and OR = 6.98; 95%CI, 1.92–25.35; $p = 0.003$, respectively); smoking history ($p = 0.002$): current and former smokers were less likely to have IV coverage than non-smokers (OR = 0.09; 95%CI, 0.02–0.40; $p = 0.002$ and OR = 0.14; 95%CI, 0.04–0.50; $p = 0.003$, respectively); and gender: women were less likely to have IV coverage than men (OR = 0.28; 95%CI, 0.09–0.90; $p = 0.032$). For PV coverage no factors were significantly associated.

Comparing to European statistics, where IV coverage in chronic medical conditions has a median rate of 50.3%[5] and no data is available for PV coverage in adults, these results are above average for IV coverage mainly in elder CRP (where IV tends to be free of charge regardless of the clinical condition for people above 64 years). Nevertheless, both IV coverage in younger patients and overall PV coverage were considerably low. The vaccination rate and the educational status are in agreement with the most prevalent educational level of our population, unveiling a possible selection bias, but also portraying our reality. Further education on IV could be of benefit to resolve the main hindrance pointed out as the reason towards non-vaccination; reimbursement issues should be discussed insofar PV non-vaccination, since already 21 European member states offer one of the 2 conjugated pneumococcal vaccines for people 50 years of age and above and/or for risk groups in certain age groups.[3]

This is the starting point of a prospective cohort study currently underway to evaluate the cost-effectiveness of both vaccines, specially pneumococcal, and to ascertain their impact on the number of infectious intercurrences, use of antibiotics (which and how long), hospitalization and deaths.

We expect, given our current data and possibly with the results of our future investigation, to increase the awareness of local physicians and administrative boards to this issue in order to develop strategies to re-enforce vaccination in CRP.

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Acute Respiratory Distress Syndrome Secondary to Histoplasmosis-induced Hemophagocytic Lymphohistiocytosis

Síndrome de distrés respiratorio agudo secundario a linfohistiocitosis hemofagocítica inducida por histoplasmosis

Dear Editor:

Acute respiratory distress syndrome (ARDS) is a condition that carries high mortality and can be caused by sepsis or pneumonia.[1] Histoplasmosis can cause a lung infection varying from mild pneumonitis to ARDS.[2] This endemic mycosis can also cause disseminated infection and is catastrophic in immunocompromised patients.[3] In transplant populations, it has an incidence of 1–3 cases per 1000 patients and is more prevalent in hepatic and renal transplants.[4–6] Hemophagocytic lymphohistiocytosis (HLH) is characterized by immune derangement of defective natural killer cells and macrophage overactivation. HLH is a rare complication of histoplasmosis but carries a mortality of up to 50%. Optimal treatment of infection-associated HLH is controversial and data is limited.[7,8] Some physicians advocate for the use immunosuppression in addition to antifungal therapy, whereas others will only treat the underlying infection. Notably, current evidence suggests that this latter approach has less mortality.[3,9–11]

We present a case of a 46-year-old Korean male who underwent a deceased donor kidney transplant in 2014 secondary to diabetic nephropathy. He presented with vomiting, diarrhea and fever and was initially treated for viral gastroenteritis. Chest X-ray (CXR) on admission showed bibasilar linear infiltrates (Fig. 1A). His clinical status rapidly deteriorated and he was admitted to the intensive care unit and was started on low-dose vasopressors. Patient's hemodynamics continued to worsen with respiratory failure requiring high-flow nasal cannula due to hypoxemia. He rapidly developed ARDS and required intubation with low-tidal volume ventilation and paralytics. Chest X-ray revealed diffuse bilateral alveolar infiltrates with air bronchogram (Fig. 1B) and chest computed tomography revealed tree-in-bud infiltrates and splenomegaly. Laboratory data was notable for pancytopenia, transaminitis, ferritin of 16,624 ng/mL, elevated LDH, normal triglycerides and a positive urine and serum *Histoplasma* antigen. He had several environmental and animal exposures including bats, rats, animal droppings and mold along subway tunnels. Work-up including acid-fast Bacilli smear and culture, hepatitis panel, *Bartonella*, *Human Immunodeficiency Virus (HIV)*, *Legionella*, *Cryptococcus*, *Parvovirus*, *Human Herpes Virus 6*, *Adenovirus*, *Epstein-barr Virus* and *Cytomegalovirus* polymerase chain reaction tests were negative. Bronchoalveolar lavage revealed numerous fungal organisms in the form of budding yeasts without evidence of pseudohyphae, consistent with *Histoplasma Capsulatum*. Culture data confirmed the diagnosis. The patient rapidly improved and was successfully extubated after starting amphotericin B, followed by itraconazole. Soluble IL-2 receptor came back elevated (14,150 pg/mL) a few days later. Tacrolimus and mofetil mycophenolate had been initially stopped due to worsening renal function but were restarted before discharge. The patient was fully recovered at 6-month follow up.

This case highlights that patients with significant immunosuppression can develop severe ARDS secondary to histoplasmosis.[2] This has mainly been described in patients with HIV who can also develop HLH as a rare complication.[3] The current treatment of primary HLH is based on immunosuppression[12] but there is not consensus on the treatment of infection-associated HLH.[8] Moreover, the literature in organ transplants patients is limited. One study reported less mortality in patients who do not receive additional immunosuppression, although only a small number of patients were included in that study.[3] Our patient met five criteria for HLH, including fever, splenomegaly, pancytopenia, high ferritin level and elevated IL2 soluble receptor. He had an excellent response to treatment targeting histoplasmosis without the use of steroids or further immunosuppression. In the largest case series of 11 cases of patients with histoplasmosis-induced HLH, the mortality was 46% at 30 days and 63% at 90 days, with increased mortality up to 80% in the group who received immunosuppression.[3] The study included nine patients with HIV and two with renal transplants.[3] Further evidence of HLH and histoplasmosis in kidney transplant is scarce. Nieto et al. report two cases, one successfully treated with antifungals alone and one with a fatal outcome after receiving increased immunosuppression.[9] Similarly, Contreras et al. report a renal transplant patient who successfully responded to antifungal therapy alone.[10] Lo et al. describe a successful experience of two kidney transplant patients who received only dual antifungal therapy with amphotericin and itraconazole.[11] Notably, there were no acute rejections in spite of decreased immunosuppression. Therefore, it should be highlighted that limiting immunosuppression may be necessary if patients are refractory to antifungal therapy to ensure complete resolution of Histoplasmosis infection. In our patient, we held immunosuppression on admission and he did not experience any complications. Limitations related to the small number of patients and the possibility of treatment bias in patients who were sicker should be considered. Prospective treatment studies would be ideal, but they are unlikely given the rarity of this disease. In conclusion, our case adds to the limited literature that suggests that treatment of an underlying infection in HLH alone could lead to rapid resolution of this otherwise lethal disorder. Further data is needed to define the role of immunosuppression in treating this condition.