



Editorial

The Future Is Now in Community-Acquired Pneumonia: Cardiovascular Complications and Conjugate Vaccines[☆]

Neumonía adquirida en la comunidad, el futuro en el presente: complicaciones cardiovasculares y vacunas conjugadas

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Recently, the ERS/ESCMID¹ and SEPAR² have published updated documents about the management of lower respiratory tract infections and community-acquired pneumonia (CAP). These are two clinically important issues that perhaps have not been sufficiently contemplated. The fact that our future actions for their treatment may be modified merits comment.

Since 1993, different authors have published many reports about expected mortality in the long-term follow-up of patients who are hospitalized for CAP. The importance of defining the causes and planning clinical procedures that modify this tendency has been underlined by several authors.³ A recent example of this is the recent study by Bordon et al.,⁴ where reduced long-term survival was confirmed in patients who are hospitalized due to CAP and after adjusting for age and comorbidity with control subjects. Until now, perhaps the most relevant finding in the literature is that, in the follow-up of patients between the ages of 41 and 80 with no significant comorbidities, there is an observed trend in mortality that is higher than expected,⁵ and that said trend correlates with the Pneumonia Severity Index.⁶

The causes of this excessive mortality have not been sufficiently clarified, although we can try to relate different observations. It is known that there are important cardiac complications in a large proportion of patients with CAP.⁷ Along this line, Perry et al.⁸ have recently published that, in a very extensive population (50 119 subjects), a significant number of patients who were followed-up for 90 days after hospitalization for CAP presented a cardiovascular event, usually during hospitalization, these being: 1.5% AMI, 10.2% congestive heart failure, 9.5% arrhythmia, 0.8% unstable angina and 0.2% stroke. Likewise, Jasti et al.⁹ reported that most re-hospitalizations after a CAP episode are the result of an underlying cardiopulmonary or neurological disease. Corrales-Medina et al.¹⁰ describe the association between acute bacterial pneumonia and acute coronary syndromes as well as the correlation between coagulation disorders and CAP.¹¹

It is known^{12,13} that persistent inflammation (defined by high circulating levels of IL-6 and IL-10) at the time of hospital discharge in patients with CAP is associated with increased post-CAP mortality. Interestingly, Kruger et al.¹⁴ report that cardiovascular biomarkers, like pro-atrial natriuretic peptide, pro-arginine vasopressin (copeptin), proendothelin-1 and pro-adrenomedullin (pro-ADM), are good predictors for CAP prognosis both in the long and short terms. Pro-ADM is the biomarker with the best behavior in this study. It has also been seen¹⁵ that mild-regional-Pro-ADM is an excellent marker for long and short-term mortality in CAP, regardless of its etiology.

Until now, we have known that patients hospitalized for CAP present a long-term mortality that is higher than expected, that patients with CAP present frequent severe cardiovascular complications and that several biological markers related with inflammation and with vascular pathology are high in CAP patients with poorer long-term prognosis. It is hard to avoid the temptation to link all these confirmed facts. Nevertheless, certain caution is required when establishing correlations and attributing them a causal origin. These reflections, in addition to previously mentioned ones, require more research to be done in this field.

In October 2011, the European Medicines Agency (EMA) approved the use of the 13-valent Prevenar13[®] (PCV13) conjugate vaccine for actively immunizing against invasive pneumococcal disease (IPD) in adults aged 50 or older. In December 2011, the Food and Drug Organization (FDA) approved its use in the prevention of pneumonia and invasive disease caused by serotypes of *S. pneumoniae* contained in this vaccine (1, 3, 4, 5, 6A, B, 7F, 9V, 14, 18C, 19A, 19F and 23F) in people over the age of 50. Clinicians now have available a 23-valent pneumococcal polysaccharide vaccine (PPV23) and a 13-valent pneumococcal conjugate vaccine (PCV13) for use in adults. Therefore, it is now necessary to update the published evidence that is available in the literature in order to reposition these vaccines in our therapeutic arsenal, knowing beforehand that we still do not have all the information available.

It is not easy to analyze all the publications written about the efficacy of a vaccine in order to establish a firm conclusion. In the case of pneumococcus, we can talk about the prevention of death, pneumonia, pneumococcal pneumonia, bacteremia and the prevention of IPD. Plus, we should not forget facts such as the rates of

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vaccine coverage in the population, the knowledge of whether the vaccine is on the vaccination calendar, or the possible influence of community immunity, a concept that we will later comment on. It is commonly accepted that PPV23 prevents IPD in adults.¹ In the classic article by Jackson et al.,¹⁶ the authors offer data about the effectiveness of PPV23 in the prevention of bacteremia, and they suggest that alternative strategies are necessary for preventing bacteremic pneumonia. A current review of the literature¹⁷ confirms that this vaccine does not seem to be effective for preventing pneumonia. In a recent 5-year follow-up study designed to analyze the efficacy of the PPV23 vaccine, Johnstone et al.¹⁸ reported that one-third of the patients who are released after a CAP episode either died or were re-hospitalized due to an infection that could have been prevented with a vaccine. Recent data in the United States and in Spain^{19,20} remind us that the load of pneumococcal disease is still very important, especially in seniors, despite the vaccine strategies followed to date.

We know some important data about the behavior of conjugate vaccines in children, in whom polysaccharide vaccines are not reliably immunogenic. After its introduction in the United States, the 7-valent conjugate vaccine (Prevenar 7[®]) was commercialized in Europe in 2001 and it became a part of the systematic calendar in the province of Madrid in November 2006. In the case of the 10-valent (Synflorix[®]), its commercialization in Europe was approved in March 2009 and it began to be commercialized in Spain on August 1, 2009. The 13-valent conjugate vaccine (Prevenar13[®]) has been approved commercially in Europe since December 2009 and it has been administered in Spain since June 2010, and is currently included in the vaccine calendars for children in the provinces of Madrid and Galicia. The introduction of the 7-valent vaccine in the pediatric population demonstrated a net reduction in the number of cases of IPD, especially of the cases produced by serotypes included in the vaccine. However, some time later an increase in IPD was observed due to non-vaccine serotypes, especially serotypes 1, 5, 19A and 7F. These serotypes are included in the 13-valent vaccine, and a clear protector effect is expected after its introduction.^{21,22} The 7-valent conjugate vaccine has likewise demonstrated its efficacy for preventing IPD in adults infected with HIV.²³

The protection provided by immune individuals to susceptible individuals by making the transmission of the disease more difficult is known as community or herd immunity. After immunization with conjugate vaccines in children, a very important reduction has been observed in pneumococcal disease by vaccine serotypes in all age groups, including in non-vaccinated patients.^{24,25} This fact is influencing the assessment (favoring conjugate vaccines) of the cost-effectiveness studies that compare PPV23 and PCV13.²⁶

Conjugate anti-pneumococcal vaccines have satisfactorily demonstrated their efficacy in children and in special adult populations. They have also shown high immunogenicity and are responsible, through group immunity, for a change in the ecology of pneumococcal disease. After their administration in adults is approved by the EMA and FDA and while knowing that there are still logistic problems to be resolved, they will play an important role in our preventive arsenal.

References

- Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect.* 2011;17 Suppl. 6:E11-59.
- Menendez R, Torres A, Aspa J, Capelastegui A, Prat C, Rodriguez de Castro F. Community acquired pneumonia. New guidelines of the Spanish Society of Chest Diseases and Thoracic Surgery (SEPAR). *Arch Bronconeumol.* 2011;46:543-58.
- Waterer GW, Rello J, Wunderink RG. Management of community-acquired pneumonia in adults. *Am J Respir Crit Care Med.* 2011;183:157-64.
- Bordon J, Wiemken T, Peyrani P, Paz ML, Gnoni M, Cabral P, et al. Decrease in long-term survival for hospitalized patients with community-acquired pneumonia. *Chest.* 2010;138:279-83.
- Waterer GW, Kessler LA, Wunderink RG. Medium-term survival after hospitalization with community-acquired pneumonia. *Am J Respir Crit Care Med.* 2004;169:910-4.
- Johnstone J, Eurich DT, Majumdar SR, Jin Y, Marrie TJ. Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. *Medicine (Baltimore).* 2008;87:329-34.
- Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Med.* 2011;8:e1001048.
- Perry TW, Pugh MJ, Waterer GW, Nakashima B, Orihuela CJ, Copeland LA, et al. Incidence of cardiovascular events after hospital admission for pneumonia. *Am J Med.* 2011;124:244-51.
- Jasti H, Mortensen EM, Obrosky DS, Kapoor WN, Fine MJ. Causes and risk factors for rehospitalization of patients hospitalized with community-acquired pneumonia. *Clin Infect Dis.* 2008;46:550-6.
- Corrales-Medina VF, Serpa J, Rueda AM, Giordano TP, Bozkurt B, Madjid M, et al. Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. *Medicine (Baltimore).* 2009;88:154-9.
- Milbrandt EB, Reade MC, Lee M, Shook SL, Angus DC, Kong L, et al. Prevalence and significance of coagulation abnormalities in community-acquired pneumonia. *Mol Med.* 2009;15:438-45.
- Martinez R, Menendez R, Reyes S, Polverino E, Cilloniz C, Martinez A, et al. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. *Eur Respir J.* 2011;37:393-9.
- Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med.* 2008;177:1242-7.
- Kruger S, Ewig S, Giersdorf S, Hartmann O, Suttrop N, Welte T. Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia: Results from the German Competence Network, CAPNETZ. *Am J Respir Crit Care Med.* 2010;182:1426-34.
- Bello S, Lasierra AB, Mincholé E, Fandos S, Ruiz MA, Vera E, et al. Prognostic power of proadrenomedullin in community-acquired pneumonia is independent on etiology. *Eur Respir J.* 2011. Nov 10 [Epub ahead of print] PMID: 22075489.
- Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med.* 2003;348:1747-55.
- Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *Can Med Assoc J.* 2009;180:48-58.
- Johnstone J, Eurich DT, Minhas JK, Marrie TJ, Majumdar SR. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. *Clin Infect Dis.* 2010;51:15-22.
- Weycker D, Strutton D, Edelsberg J, Sato R, Jackson LA. Clinical and economic burden of pneumococcal disease in older US adults. *Vaccine.* 2010;28:4955-60.
- Gil-Prieto R, Garcia-Garcia L, Alvaro-Meca A, Mendez C, Garcia A, de Miguel AG. The burden of hospitalisations for community-acquired pneumonia (CAP) and pneumococcal pneumonia in adults in Spain (2003-2007). *Vaccine.* 2011;29:412-6.
- Picazo J, Ruiz-Contreras J, Casado-Flores J, Giangaspro E, Del Castillo F, Hernandez-Sampelayo T, et al. Relationship between serotypes, age, and clinical presentation of invasive pneumococcal disease in Madrid, Spain, after introduction of the 7-valent pneumococcal conjugate vaccine into the vaccination calendar. *Clin Vaccine Immunol.* 2011;18:89-94.
- Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis.* 2011;11:760-8.
- French N, Gordon SB, Mwalukomo T, White SA, Mwafurirwa G, Longwe H, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med.* 2010;362:812-22.
- Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998-2004. *J Infect Dis.* 2007;196:1346-54.
- Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis.* 2010;201:32-41.
- Smith KJ, Wateska AR, Nowalk MP, Raymond M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. *J Am Med Assoc.* 2012;307:804-12.