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Editorial

Pneumonia in children: The role of rapid diagnostic tests for virus in antimicrobial stewardship

Neumonía en niños: el papel de las pruebas de diagnóstico rápido de virus en la administración de antimicrobianos

Pneumonia is considered as the single largest cause of death in children under the age of five years, causing more than 800,000 deaths every year worldwide. However, global efforts have led to a decrease of 30% in the incidence of pneumonia in children and by 50% in mortality during the Millennium Development Goal period.[1] Socioeconomic development, preventive interventions, improved access to care and quality of care in hospitals were key factors to achieve these goals. Focusing on recent vaccine implementation strategies, most countries have introduced the pneumococcal conjugate vaccine (PCV) in their childhood immunization programs, which has led to a substantial reduction in pneumococcal disease.[2]

There was also important progress fighting against pneumonia in developed countries. In Spain, the incidence rates of community-acquired pneumonia (CAP) hospitalizations decreased among children from 2001 to 2014, mainly in those younger than 2 years old. Overall crude in-hospital mortality fell from 4.1‰ to 2.8‰. Once again, improvement in PCV vaccination coverage seems to have an effect on hospitalizations and outcomes for CAP in children.[3]

Prospective studies were carried out recently to reveal the causes of pneumonia in the PCV era. The PERCH study was an impressive effort of collaboration that enrolled more than 1700 children with severe or very severe pneumonia according to WHO classification with a positive chest-X-ray in seven countries of Africa and Asia from 2011 to 2014. Viruses caused most of the severe pneumonia cases (61%), and RSV was the leading pathogen (31%) at all sites. *Streptococcus pneumoniae* represented 6.7% of all cases globally.[4] The EPIC study was a multicenter, prospective, population-based study of community-acquired pneumonia requiring hospitalization among children in the United States of America from 2010 to 2012. Among 2222 children with radiographic evidence of pneumonia, a viral or bacterial pathogen was detected in 1802 (81%), one or more viruses in 1472 (66%), bacteria in 175 (8%), and both bacterial and viral pathogens in 155 (7%). The most commonly detected pathogen was RSV (in 28% of the children). *S. pneumoniae*, *S. aureus*, and *S. pyogenes* were detected in 4%,1% and 1% respectively.[5] The main result of these studies is that respiratory viruses, mainly RSV, are currently the most common causes of pneumonia in any child who requires admission to a hospital worldwide.

The rapid identification of respiratory viruses in children with pneumonia presenting for hospital care may result in favorable interventions, such as a prescription of an early and appropriate antiviral, -when indicated-, aiding on decisions on hospital admissions, but also optimizing infection-control practices. Rapid antigen-based tests are not adequately accurate. However, there are also commercially multiplex molecular diagnostics for respiratory viruses with rapid turn-around time (TAT).[6] These rapid diagnostic testing (RDT) provide accurate results for respiratory viruses when compared to the best available reference standard.[7]

If we could properly identify a virus as the cause of a respiratory infection, we could thereafter reduce the prescription of inappropriate antibiotics. Although most respiratory infections are caused by viruses, antibiotics are frequently overprescribed in this setting. The most common antibiotic prescribed in children with a respiratory infection is a β lactam antibiotic. Nasrint et al. observed in a prospective cohort of 461 children that the carriage of penicillin-resistant pneumococci was significantly associated with the use of β lactam antibiotics in the previous two months. In this study, the modelled odds of carrying penicillin-resistant pneumococcus was 4% higher for each additional day of use of β lactam antibiotics.[8]

Several studies have given insights into the use of RDT to achieve stewardship principles in children. A Cochrane review published in 2014 and based on four studies involving 759 previously healthy children coming to the Emergency Department with fever and respiratory symptoms, observed that the use of rapid viral tests showed fewer antibiotic prescriptions trend, but this finding was not statistically significant.[9] More recently, a controlled clinical trial in 583 children admitted to hospital with suspected acute respiratory infections (mainly RSV) in the Netherlands, could not show either a benefit in antibiotic use when RDT results were rapidly communicated to the clinicians.[10] However, other observational studies have reported significant reductions on the use of antibiotics[11] and finally, there are also favorable

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international recommendations for the use of RDT; the guidelines of the Infectious Diseases Society of America for the management of CAP in children stated that testing for respiratory viruses can modify clinical decision making including the prescription of antibacterial therapy.[12]

In this issue of *Enfermedades Infecciosas y Microbiología Clínica*, Aguilera Alonso et al.[13] described the experience of early identification of respiratory viruses in 100 children (median age of 21 months) with 105 episodes of CAP in a tertiary hospital in Madrid. This was an observational, retrospective study of children admitted to care management from 2014 to 2018. In a step-by-step approach, a rapid antigen-based test, for RSV and influenza A and B, and a multiplex molecular diagnostics respiratory viruses (Clart® Pneumovir, Genómica S.A.U., Madrid, España) were used. All children included had x-ray findings of pneumonia. *S. pneumoniae* was isolated in blood culture of one child. There was an identification of a respiratory virus in 93 (88%) cases, mainly RSV in 37 (35%) cases, and influenza in 21 (20%) cases. Patients with RSV detection had a lower onset of empirical antibiotic therapy (35.1% vs 55.9%, $p = 0.042$). The duration of antibiotic therapy in cases with no viral identification was higher than in those with RSV or influenza identification (68.8% received antibiotics more than 2 days vs 45.6%, respectively, $p = 0.017$).

This study represents a contribution on the potential opportunities of RDT implementation strategies towards achieving antimicrobial stewardship. It is also an important recall of the work to be done on the improvement in Antibiotic Stewardship Programs for respiratory infections in children in our country. Spain continues to be among the countries with the highest antibiotic consumption in Europe.[14] Prescriptions of antibiotics to children in Spain remains also high and antibiotics for respiratory infections are of the most prescribed.[15]

Aguilera Alonso et al reported that empiric antibiotics were used in 51 cases (48.6%). Interestingly, viral tests were done in the first 48 h after admission and the testing TAT had a maximum time of 24 h. Previous studies have suggested that even shorter TAT could have more impact. Shorter TATs have been related to decreased antibiotic use, early antibiotic discontinuations, decreased length of stay, and also decreased costs in randomized controlled trials in adults.[16,17]

In addition, about 15% of the cases with RSV or influenza identification were admitted without antibiotic therapy but started on antibiotics later. This result may illustrate the concerns of clinicians about a possible bacterial-viral co-infection in a patient with a severe respiratory infection. Viral co-detection was observed in half of the patients with bacterial pneumonia in EPIC study, and specifically, in 82% of the cases of pneumococcal pneumonia a virus was also identified.[6]

The main limitation of etiologic pneumonia studies is that it is very hard to identify the final cause of pneumonia in children. Only in a minority of cases, we can isolate or identify the pathogen in the lung, lower respiratory tract or blood. The detection of pathogens in nasopharyngeal or oropharyngeal swabs with the use of a molecular method could represent infection limited to the upper respiratory tract or convalescent-phase shedding, and thus detection may not denote causation.[6] No current diagnostic test is adequately sensitive to exclude bacterial–viral coinfection when a virus is detected. In clinical practice, biomarkers such as procalcitonin or C-reactive protein may help in ruling out bacterial infection when the levels are low.[18]

Finally, in the next years, we will have the opportunity of evaluating the impact of important preventive interventions on the morbidity and mortality of pneumonia in children which surely will be reflected in antibiotic consumption. First of all, a great effort need to be made to increase influenza vaccination uptake in vulnerable population. Low levels of influenza vaccination remains a concern. It is also important to consider that the impact of influenza vaccination in disease prevention may be higher with the administration of inactivated quadrivalent influenza vaccine (IIV4). IIV4 provides a broader protection against influenza. In a phase III, observer-blind trial, including more than 12,000 children from 6 to 35 months of age, IIV4 was related to the reduction of antibiotic use associated with influenza illness by 71% in the group of European children.[19] The impact of PCV in pneumonia, previously commented, maybe notorious in Spain with the recent inclusion of PCV13 in the National Immunization Program. There are also an urgent need and an important pipeline of development with RSV vaccine candidates that are been evaluated in children but also in pregnant women, which could lead to safeguarding their infants in the first few vulnerable months of life.[20]

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