Efficacy and safety of a decision rule for using antibiotics in children with pneumonia and vaccinated against pneumococcus. A randomized controlled trial

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ABSTRACT

Introduction. Although most cases of pneumonia in children younger than 5 years old have a viral nature, in everyday practice, they are frequently treated with antibiotics. A clinical decision rule (BPS:Bacterial Pneumonia Score) proved to be effective for identifying which children with pneumonia required antibiotics, but its performance has not been assessed in the population vaccinated against pneumococcal disease.

Our objective was to assess whether using the BPS would allow to reduce antibiotic use compared to routine management of children with community acquired pneumonia vaccinated against pneumococcal disease.

Material and Methods. Randomized, controlled, partially-blinded clinical trial with parallel groups comparing two approaches in the management of children aged 3-60 months old in an outpatient setting because of pneumonia, who had been vaccinated with the pneumococcal conjugate vaccine.The BPS group received antibiotics with a BPS ≥4 points; while the control group was administered antibiotics at the discretion of the treating physician. The estimated sample size was calculated as, at least, 30 patients per group. The rate of antibiotic use and the clinical course were compared in both groups.

Results. Sixty-five patients (33 in the BPS group and 32 in the control group) were included; their average age was 17.5 months old. Antibiotic use was significantly higher in the control group than in the BPS group (21/32 versus 9/33; OR: 5.09; 95% CI: 1.57-16.85; p= 0.001). Seven patients had an unfavorable course (three in the BPS group, and four in the control group).

Conclusion. The use of the BPS allowed to reduce antibiotic use in the initial management of patients with pneumonia vaccinated against pneumococcal disease, without increasing the probability of an unfavorable course of the disease.

Key words: *pneumonia, respiratory tract infections, decision support techniques.*

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INTRODUCTION

Pneumonia is still a major cause of child morbidity and mortality, with an annual incidence of 36-40 events/1000 children younger than 5 years old.[1]

Although in this age group, most pneumonia cases are viral,[2] since no etiological diagnosis is possible during the visit, there is a risk for overdiagnosing bacterial infection and, therefore, prescribing an unnecessary antibiotic therapy. This leads to an increase in bacterial resistance, costs and the risk for adverse events.[3]

Indirect indicators of etiology may be used, including different epidemiological (season, age), clinical (temperature, respiratory signs), laboratory (leukocytes, erythrocyte sedimentation rate), and imaging test (chest X-ray) factors, but none of them separately is effective to predict etiology.

The so-called clinical prediction models, that combine several elements, have been successfully used for diagnostic or prognostic purposes in different clinical situations.[4] In 2006, Moreno, et al. designed a predictive model (Bacterial Pneumonia Score, BPS), which allowed to accurately identify patients with pneumonia who would not benefit from antibiotic use.[5] This tool has been adequately and prospectively validated and has even been assessed in outpatients.[6] Moreover, the impact of the BPS on antibiotic use has been assessed in a controlled clinical trial,[7] thus complying with the best development standard for this type of clinical management tools.[8,9]

However, all trials that included BPS development, validation and impact assessment were designed before 2012. In 2012, the 13-valent

pneumococcal conjugate vaccine (Prevenar 13[MR]) was introduced in the national immunization schedule of Argentina for infants younger than 2 years old. There is evidence that its mass introduction may remarkably change the epidemiological pattern of pneumonia.[10, 11]It is reasonable to believe that this vaccine may have an impact on the performance already demonstrated by this prediction rule.

The objective of this article was to assess whether using the BPS clinical decision rule for the initial management of patients with pneumonia would allow to reduce antibiotic use compared to the routine management of this disease without increasing treatment failure rate in a population who has received the pneumococcal conjugate vaccine.

POPULATION AND METHODS

Randomized, controlled, partially-blinded trial with parallel groups comparing two management approaches (BPS and routine management) for patients with pneumonia.

Three to sixty month-old infants seen at the outpatient clinic of Hospital General de Niños Pedro de Elizalde (HGNPE) diagnosed with pneumonia (fever, cough, tachypnea and compatible auscultatory findings) were included,[12] with a 24-48 hour course, complete pneumococcal conjugate vaccination series and signed informed consent. Patients with wheezing, severe or very severe pneumonia,[1] incomplete immunization, chronic heart or pulmonary disease, pleural effusion, lung abscess, hospitalization requirement, liver or kidney failure, Down's syndrome, antibiotic treatment or hospitalization in the previous two weeks were excluded.

The study lasted one year (from April 1st, 2013 to March 31st, 2014).

All patients diagnosed with pneumonia at the general practice offices of HGNPE were referred to one of the investigators to be examined. Those who met all inclusion criteria and none of the exclusion criteria were invited to participate. Afterwards, each patient was assigned to one of the management approaches (BPS or routine management). The investigator was in charge of randomization using a sealed envelope method.

Patients in the control group were assigned to a treating physician as per the appointment system. This physician decided on management, additional procedures and eventual antibiotic use based on the hospital's clinical practice guidelines which consider an initial empiric treatment with antibiotics (amoxicillin: 80-100 mg/kg/day) for every patient younger than 5 years old with a likely bacterial pneumonia managed in an outpatient setting.[13]

Patients assigned to the study group (BPS) were followed by the investigator and underwent clinical examination, axillary temperature measurement, complete blood count and chest X-ray, and their BPS score was estimated. BPS points range from -3 to 15 points[5] (*Figure 1*). An antibiotic was prescribed (amoxicillin: 80-100 mg/kg/day)[14] to those with a BPS ≥4 points. Expectant management was adopted for patients with a BPS <4.

In both groups, patients were asked to return for follow-up by another investigator, blinded to the treatment group, who assessed their clinical course in the first 24 h and at 48 ± 12 h, 5 ± 1 days, 7 ± 1 days, and 10 ± 1 days, and verified the primary (antibiotic use) and secondary (clinical course) outcome measures every time. For patients who did not meet adequate clinical course criteria, treatment with a first-line antibiotic was prescribed, if they were not already receiving one, or a second-line antibiotic was prescribed, if they were already receiving an antibiotic; if necessary, hospitalization was indicated.

The primary outcome measure was the rate of antibiotic use in both groups. The secondary outcome measure was the clinical course, defined as adequate if the following criteria were met: lowering of fever within 48 h, normal respiratory rate or reduction of more than 5 breaths/minute within 48 h, no signs of severe pneumonia, not requiring hospitalization or antibiotic use, or antibioticshifting if antibiotics were initially used. The final assessment was conducted on Day 7. Outcome measures were considered categorical (adequate or unfavorable clinical course).

In order to assess whether both groups were comparable, age, sex and axillary temperature were used as control variables.

Sample size: Expecting to reduce antibiotic use ≥40% between the BPS and control groups (86% versus 46%),[7] the sample size was estimated at 26 patients per group, with a power of 80%, and a two-tailed alpha error of 0.05. It was considered to recruit 30 subjects per group taking into account potential losses to follow-up and a study extension of, at least, one more year in order to prevent epidemiological biases.

Statistical analysis: Value distribution was

described as mean and standard deviation for numerical outcome measures, and as percentages and 95% confidence intervals (95% CI) for categorical outcome measures. For group comparison purposes, a t-test for independent samples, and a chi square test were used, as applicable. The rate of antibiotic use and an unfavorable clinical course was estimated for each group and compared using a chi square test. Odds ratios (ORs) and 95% CIs were estimated. For all cases, a p value <0.05 was considered significant. The SPSS 11.0 software, Chicago, USA, 2001 was used.

Ethical considerations: The study followed Good Clinical Practice Guidelines, the Declaration of Helsinki and community and national rules in force, and was approved by the institutional review boards. The informed consent of all participants was requested and obtained. A Safety Monitoring Board was responsible for assessing the development of severe adverse event and treatment failure rates periodically. The study was registered in clinicaltrials.gov (NCT01875731).

RESULTS

Sixty-five patients were included (BPS group: 33; control group: 32) (*Figure 2*). Of these, 32 were female; their average age was 17.5 ± 10.5 months old (range: 3.3-49 months old). Average axillary temperature was 38.5 ± 0.4 ºC (range: 38-39.2 ºC). More than half of the patients had received three vaccine doses (the third one was a booster dose) (*Table 1*).

No differences were observed between patients in the BPS group and the control group in terms of age (17.2 ± 10.2 months old versus 17.5 ± 11 months old; p = 0.83), axillary temperature (38.5 ± 0.4 ºC versus 38.6 ± 0.4 ºC; p = 0.23) or sex distribution (male patients: 19/33 versus 14/32; OR: 1.06; 95% CI: 0.35-3.06; p = 0.88) *(Table 1)*.

BPS analysis showed a minimum score of -2 and a maximum score of 9; 24/33 patients had a score of less than 4 points.

Forty-six percent (30/65) of patients received antibiotic therapy. Antibiotic use as the initial management for pneumonia was observed in 9/33 patients in the BPS group and in 21/32 in the control group (OR: 5.09; 95% CI: 1.57-16.85; p= 0.001).

Clinical course was unfavorable in 7/65 patients (10.7%) (acute otitis media: 3; acute gastroenteritis: 4). Patients with an unfavorable clinical course corresponded to 3 in the BPS group, and 4 in the control group (OR 0.7; IC 95%: 0.1-4.19; p = 0.71). Among patients with an unfavorable outcome, 4 had not received antibiotics (2 in each group).

FIGURE 1. *BPS (Bacterial Pneumonia Score). Clinical decision rule for antibiotic use in children younger than 5 years old with community acquired pneumonia*

Predictor			**Puntos**
Axillary temperature ≥39 ºC			3
Age ≥9 months old			2
Absolute neutrophil count ≥8000/mm^3			2
Bands ≥5%			1
X-ray	Infiltrate	Well-defined, lobar, segmental	2
		Poorly-defined, patchy	1
		Interstitial, peribronchial	-1
	Location	Single lobe	1
		Multiple lobes in one or both lungs, but well-defined	1
		Multiple sites, peribronchial and poorly-defined	-1
	Pleural effusion	Minimal	1
		Obvious	2
	Abscess, bullae or pneumatocele	Equivocal	1
		Obvious	2
	Atelectasis	Obvious	-1
		Lobar, involving right medium lobe or right upper lobe	-1
		Lobar, involving other lobes	0
Total score			-3 to 15

BPS (Bacterial Pneumonia Score) ≥ 4 points= antibiotic prescription.

DISCUSSION

Patients with pneumonia vaccinated against pneumococcal disease, whose treatment was decided based on their BPS, received antibiotics much less frequently than those treated at the discretion of their treating physician. Such evident reduction in antibiotic use was verified without increasing the treatment failure rate.

Although there is plenty of evidence that a high rate of childhood pneumonias are caused by viral infections,[15] the most important clinical practice guidelines include an empiric and systematic use of antibiotics. This was particularly evident in the World Health Organization (WHO) guidelines,[12] which specifically described that every child with pneumonia should receive antibiotics. Subsequently, the Argentine Society of Pediatrics (SAP),[14] the British Thoracic Society (BTS),[1] the Infectious Disease Society of America (IDSA)[2] and the American Academy of Pediatrics[16] introduced, in their respective guidelines, considerations on the high prevalence of viral etiology among childhood pneumonia cases, especially in the first two years of life. However, all these guidelines agree on the need to use antibiotics when no etiological diagnosis can be made.

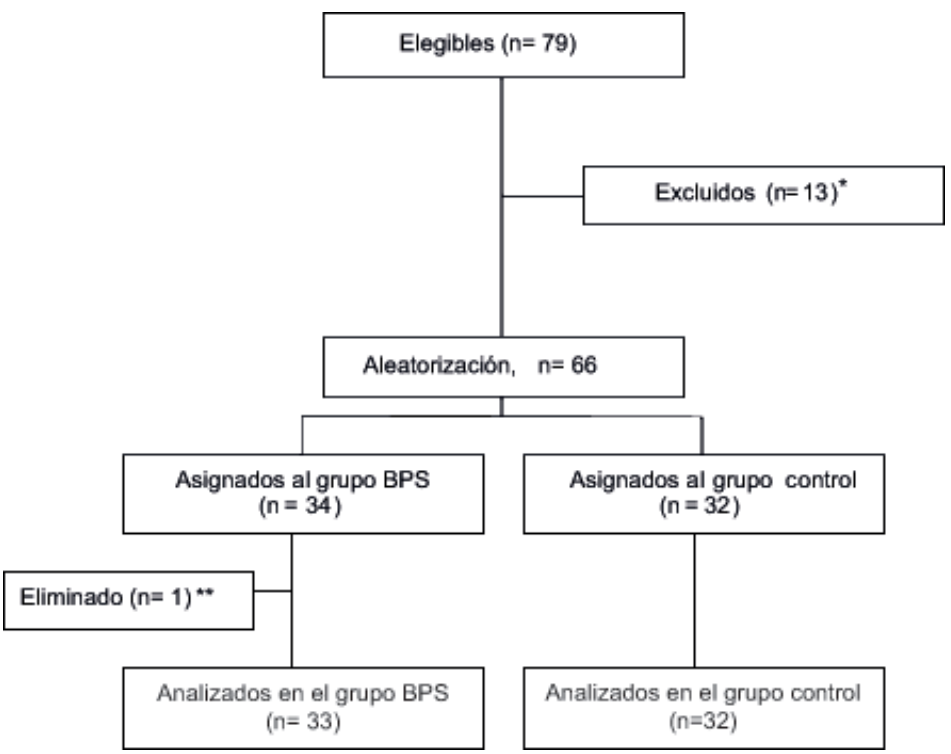
Such difficulty to adequately identify the etiology of pneumonia in children has resulted in a significant inadequate antibiotic use leading to increased bacterial resistance, health costs and prevalence of adverse events.

There is evidence that a significant rate of children with acute respiratory tract infections are treated with antibiotics, although usually of viral nature. In Argentina, 90% of pneumonia cases[17] and 48% of bronchiolitis cases were managed with antibiotics.[18]

This is not very different from what occurs in the United States, where most community-acquired pneumonias in children are treated with antibiotics, and 80% of them inadequately receive broad spectrum antibiotics.[19]

There is evidence that antibiotic use in respiratory tract infections causes a 4-fold increase in antibiotic-resistant bacteria carriage and favors the conditions for the use of second-line antibiotics.[20]Conversely, it has been demonstrated

FIGURE 2. *Patient randomization scheme*



* Age (2), skin rash (1), lack of vaccination card (5), preterm infant (1), incomplete immunization schedule (4).
** Lab test was not possible.

that reducing inadequate antibiotic use may help to diminish bacterial resistance.[21]

The extent of this problem is far from reaching a stable point, but is dangerously and continuously increasing. The number of hospitalizations for infections with verified antibiotic resistance increased 359% in the 1997-2006 decade, and a higher increase has been observed in children and youth younger than 18 years old.[22] Considering the values from the National Committee on Clinical Laboratory Standards (NCCLS) before 2008, the occurrence of penicillin-resistant *Streptococcus pneumoniae* increased in most Latin American countries, while it has doubled in Argentina between 1994 and 1998 (20.6% to 44.4%).[23] Fortunately, such increase in *"in vitro"* resistance did not result in increased penicillin treatment failure in children hospitalized for pneumonia.[24]

Exclusively using clinical elements to diagnose pneumonia (cough and tachypnea)[12] implies that many children with a normal X-ray are diagnosed with pneumonia.[25] A chest X-ray is an easily-accessible and low-cost diagnostic method that may improve diagnostic specificity.

Although the capacity of a chest X-ray to predict etiology for pneumonia has been questioned,[26] X-ray use as a standard assessment method has increased. In this regard, Swingler[27] has recognized that the chest X-ray assessment method established by Khamapirad[28] is the only one capable of distinguishing between viral and bacterial etiology. This chest X-ray assessment has proven to have an adequate diagnostic capability to identify bacterial pneumonia[29] and is the one used by the BPS.

The extent of agreement among observers may be considered an indirect assessment of a chest X-ray's diagnostic capability.[30] A simple and standardized X-ray interpretation allows to unify criteria and, as a result, obtain an adequate extent of agreement among observers.[31] In addition, the Khamapirad method has demonstrated an excellent specificity,[32] probably due to the negative points assigned to certain items (for example, interstitial infiltrate, atelectasis) *(Figure 1)*.

Lastly, unlike those methods exclusively based on a chest X-ray to infer the etiology of pneumonia,[33] the BPS includes clinical and laboratory items that increase its specificity.[34]

In spite of the several clinical prediction rules available in child health, few are used in everyday practice. Their limited use is possibly related to the mistaken expectation that clinical prediction rules should be 100% sensitive (actually only a few have a >90% sensitivity). It is important to note that an adequately developed and validated clinical prediction rule, even though far from perfect, will always be more sensitive than clinical criterion itself;[35] even more, if the prediction tool has been modified using a controlled clinical trial, as is the case of the BPS.

Our study has certain strengths that should be taken into account. On one hand, it was developed throughout one year and this allowed to reduce the bias that the occasional circulation of several microorganisms may have if a shorter period had been considered. In addition, the best possible design (randomized and blinded to the investigator) was chosen to prove the performance of a clinical decision rule[8,9] and together with a

TABLE 1. *Comparison between study group and control group*

	Study group (n= 33)	**Control group (n= 32)**	**Significance**
Gender (male)	19/33	14/32	0.88*
Age (months)	17.2 ± 10.2	17.5 ± 11	0.83**
Temperature (ºC)	38.5 ± 0.4	38.6 ± 0.4	0.23**
Number of pneumococcal vaccine doses			
- 1 dose	2	-	-
- 2 doses	8	10	-
- 3 doses***	23	22	-
Antibiotic use	9/33	21/32	0.001*
Unfavorable clinical course	3/33	4/32	0.71*

* Chi square test.
** T-test for independent samples.
*** The last one is a booster dose.

powerful outcome measure that would assess the effectiveness of the studied tool beyond doubt. Finally, patient follow-up was excellent (no losses to follow-up), and this warrants that BPS use is safe for the chosen scenario.

On the other hand, the study has potential weaknesses that should be considered. No microbiological screening was performed in any patient; however, such screening is not included in any of the guidelines for patients with pneumonia managed on an outpatient basis.[15,16] Likewise, although the study was conducted at a specialized hospital, all patients had spontaneously attended the hospital and were potential candidates for an initial outpatient management.

Lastly, BPS systematic use may help to limit inadequate antibiotic use and its consequences (resistance, costs, adverse events), even in children who have received the pneumococcal vaccine.

CONCLUSION

Patients with pneumonia and vaccinated against pneumococcal disease, whose treatment was decided based on their BPS, received antibiotics in 50% of cases when compared to those treated at the discretion of their treating physician. Such evident reduction in antibiotic use was verified without increasing the treatment failure rate. ■

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