A Tool to Distinguish Viral From Bacterial Pneumonia

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Background: Establishing the etiology of community-acquired pneumonia (CAP) in children at admission is challenging. Most of the admitted children with CAP receive antibiotics. We aimed to build and validate a diagnostic tool combining clinical, analytical and radiographic features to differentiate viral from bacterial CAP, and among bacterial CAP, typical from atypical bacteria.

Methods: Design—observational, multi-center, prospective cohort study was conducted in 2 phases. Settings: 24 secondary and tertiary hospitals in Spain. Patients—A total of 495 consecutive hospitalized children between 1 month and 16 years of age with CAP were enrolled. Interventions—A score with 2 sequential steps was built (training set, 70% patients, and validation set 30%). Step 1 differentiates between viral and bacterial CAP and step 2 between typical and atypical bacterial CAP. Optimal cutoff points were selected to maximize specificity setting a high sensitivity (80%). Weights of each variable were calculated with a multivariable logistic regression. Main outcome measures—Viral or bacterial etiology.

Results: In total, 262 (53%) children (median age: 2 years, 52.3% male) had an etiologic diagnosis. In step 1, bacterial CAPs were classified with a sensitivity = 97%, a specificity = 48%, and a ROC's area under the curve = 0.81. If a patient with CAP was classified as bacterial, he/she was assessed with step 2. Typical bacteria were classified with a sensitivity = 100%, a specificity = 64% and area under the curve = 0.90. We implemented the score into a mobile app named Pneumonia Etiology Predictor, freely available at usual app stores, that provides the probability of each etiology.

Conclusions: This 2-steps tool can facilitate the physician's decision to prescribe antibiotics without compromising patient safety.

Key Words: community-acquired pneumonia, typical bacteria, atypical bacteria, viral pneumonia, antibiotic stewardship

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Community-acquired pneumonia (CAP) is a significant cause of morbimortality worldwide.[1–3] Common etiology are viruses and bacteria.[4–6] However, when an individual patient is attended, etiology is rarely ascertained in a short time. Therefore, pediatricians have to decide empirically if a child needs antibiotics. As a result, most children receive antibiotics.[4,7]

We hypothesized that a 2-steps score built from clinical, radiographic and analytical features would differentiate most typical bacterial CAP accurately from viral and atypical bacterial CAP. The aim of this study was to build and validate a diagnostic tool to sequentially differentiate viral from bacterial CAP, and among bacterial CAP, typical from atypical bacteria.

METHODS

Study Design

This observational, multi-center, prospective cohort study was conducted in 2 phases. The first pilot phase was performed at 2 hospitals in Madrid, Spain, from April 2012 to March 2015. The second phase was conducted in 15 hospitals in 3 regions of Spain (Madrid, País Vasco and Andalucía), from December 2017 to May 2019.

Both phases were approved by the Ethics Boards of Hospital Universitario Ramón y Cajal (first phase, code 2011/0025) and Hospital 12 de Octubre (second phase, code 17/311) and the other participating hospitals. Informed consent was obtained from the guardians of all patients. Adapted information was given and assent was obtained from patients from 12 to 16 years.

Participants

Eligible participants were children between 1 month and 16 years of age admitted to any of the participating hospitals, diagnosed as radiographically confirmed CAP, during the recruitment period. Enrollment was performed continuously until reaching a convenience sample of 150 participants in the first phase and 300 participants in the second phase, and a 10% of potential lost to follow-up. CAP was defined as fever and a compatible image in the chest radiograph (CXR) at admission. The interpretation of the CXR was performed following the standards of the "WHO Vaccine Trial Investigators Radiology Working Group."[8] These standards establish 3 possible interpretations: "consolidation" (including consolidation and/or pleural effusion) and "other infiltrates," or "normal." Pleural effusion was confirmed with ultrasonography.

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CAP was identified in the CXR by the attending pediatrician who admitted the participant and confirmed by radiologists at each center. Exclusion criteria were the following: immunosuppressive conditions, chronic cardiac or pulmonary disease (except asthma), hospital admission in the previous 30 days and suspicion of lung aspiration or foreign body in the airway. Participants were followed up until discharge.

Microbiologic Procedures

An extensive microbiologic workup was performed. In short, we did blood cultures, *Streptococcus pneumoniae* antigen (BinaxNow) and/or polymerase chain reaction (PCR) for *S. pneumoniae* in pleural fluid (PF) if thoracentesis was performed, PCR in blood for *S. pneumoniae* and other typical bacteria, PCR in nasopharyngeal aspirate (NPA) for 16 viruses: respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenza virus 1, 2, 3 and 4, influenza virus (A and B), human Bocavirus (hBoV), adenovirus (ADV), enterovirus (EV), rhinovirus (RhV), and human coronavirus (hCoV) 229E, OC43, NL63 and HKU12. The commercial systems xTAG Respiratory Viral Panel Fast v1 (Luminex Molecular Diagnostics, Toronto, Canada, 96% of participants) and CLART Pneumovir (Genomica SAU, Coslada, Spain, in 4% of participants) were used. PCR for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* was also performed using Mych Real Cycler–BIO-RAD CFX96, Progenie Molecular, Easy Mag (Biomérieux), and Mychle Real Cycler–BIO-RAD CFX96, Progenie Molecular. In all molecular tests, an internal extraction-amplification control was included to detect false negatives by PCR inhibition. Two paired samples for serology (at admission and 2–4 weeks afterwards) of *M. pneumoniae* and *C. pneumoniae* were performed throughout enzyme immunoassay in 96-well plates, automated on Dynex platform and according to manufacturing companies' protocols: Vircell, detection of IgG and IgM antibodies to *C. pneumoniae* and detection of IgG antibodies to *M. pneumoniae* and Palex Medical, detection of IgM antibodies to *M. pneumoniae*.

Definition of the Etiologic Agent

The types of CAP were defined as:

1. Likely typical bacterial infection: a bacterial pathogen (*S. pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae*, among others) detected in the blood through culture or PCR, or in PF, through culture, PCR or *S. pneumoniae* antigen detection. *Staphylococcus epidermidis* and other pathogens typically considered contaminants in healthy children were excluded.
2. Likely atypical bacterial infection: *M. pneumoniae* or *C. pneumoniae* detected by PCR in NPA or seroconversion or significative increase in IgG titles in the second sample.
3. Likely viral infection: at least one putative pathogen respiratory virus (RSV, Influenza, parainfluenza virus, hMPV) detected in NPA by PCR, and lack of (1) or (2). Other respiratory viruses (hRV, ADV, EV, hCoV, hBOV) were not included as likely viral infections due to poor specificity for CAP.[5,9,10]
4. In case of a positive putative virus detected in addition to bacteria, CAP was classified as bacterial, since the final purpose of the study was to identify which patients would need antimicrobials.

Databases

A manual selection based on clinical congruence of possible variables which predict the etiology of pneumonia was made (n = 18). They were radiographic image, gender, pneumococcal conjugate vaccine, influenza vaccine, fever days at admission, age at admission, vomiting, cough, work of breathing (WoB), respiratory rate, maximum temperature, wheezing, oxygen saturation, lymphocyte count, leukocytosis >15,000 or leukopenia <4000 cells/mm^3, neutrophilia >10,000 cells/mm^3, hemoglobin in blood and sodium, albumin, C-reactive protein (CRP) and procalcitonin in plasma. Subjective variables or those difficult to collect were excluded.

Statistical Analysis

The categorical variables were presented as frequency distributions and the continuous variables were presented as median and interquartile ranges. To assess differences, we performed a chi-squared test for categorical variables and the Mann-Whitney *U* test for continuous variables.

The complete dataset was randomly split into a training set with 70% of the registers (n = 184) and the remaining 30% for testing (n = 78). This partition was balanced based on the etiology (bacterial and viral).

The predictive relative variable importance for predicting bacterial and typical bacterial etiology was assessed by a Ridge regression model. The variables with more than 10% of relative importance were selected to be included in the score.

For each of the steps of the score, the selected continuous variables were categorized using the optimal bootstrapped cutoff points selected by maximizing specificity while maintaining sensitivity above 80% for detecting bacterial etiology.

The score was built using 2 multivariable logistic models. In the first step, we extracted the odds ratio (OR) for variables associated with bacterial etiology (ref.: viral etiology) in the training set. Afterwards, we selected only the patients with bacterial etiology from the training set (n = 87) and extracted the OR for variables assessing the risk of typical bacterial compared with atypical bacterial etiology. Those variables with few outcome events per level and/or large OR with a wide confidence interval (infinite or +1000) were excluded to avoid sparse data bias. Finally, the total score was calculated for each subject to represent the prediction of the etiology probability. The optimal cut-point of each step was selected by maximizing specificity while maintaining sensitivity above 80% for bacterial etiology and typical bacterial etiology, respectively. Both steps of the score were externally validated in the testing dataset. The performance of each score was assessed by describing the sensitivity, specificity, accuracy and area under the curve (AUC).

The missing values of both partitions (training/testing) were imputed using a nonparametric algorithm based on random forest. The normalized root mean squared error and the proportion of falsely classified were assessed for continuous and categorical variables, respectively. All the statistical analyses were performed using the R language.

Mobile app

We implemented the score into a decision support tool mobile app to make the etiologic classification comprehensive, easy and friendly to the physicians. The app provides the probability of each etiology, and the user should interpret it as a guide for treatment. The app is freely available at Apple Store and Android named Pneumonia Etiology Predictor (VALS-DANCE). The web app is also available at https://rserver.h12o.es/pediatria/VALSDANCE/(username: user, password: 0000) (see video, Supplemental Digital Content 1, http://links.lww.com/INF/E532).

RESULTS

A total of 495 patients were enrolled, 151 in phase 1 and 344 in phase 2. Of them, 465 (94%) received antibiotics at admission and 371 (74.9%) completed all the tests and the follow-up. At least a likely causative pathogen was identified in 262 patients (52.9%). A total of

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138 (52.7%) were attributed to viral etiology and 124 (47.3%) to bacterial etiology. Of them, 40 (15.3%) were attributed to typical bacteria and 84 (32.1%) were attributed to atypical bacteria (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/E533).

The predictors included in the first step of the score, which aims to classify bacterial from viral etiology are displayed in Table 1 and plotted by importance in Figure, Supplemental Digital Content 3, http://links.lww.com/INF/E534.

According to the optimal cutoff point, age at admission was categorized as ≥3 years for both steps, hemoglobin was categorized as ≥11 g/dL in both score steps, and maximum temperature was categorized as ≥37.7 °C in step 1.

The predictors included in the second step, which aims to classify typical from atypical bacterial etiology are also displayed in Table 1 and plotted by importance in Figure, Supplemental Digital Content 4, http://links.lww.com/INF/E535.

Step 1 (Viral vs. Bacterial Community-acquired Pneumonia)

The weights for each level and variable of the score were calculated from the OR in the multivariable model. The step 1 discriminated bacterial CAP using the information of: CXR (consolidation, +5.5 points), age at admission (≥3 years, +10.6), WoB (lack of WoB, +2.2), wheezing (no wheezing, +1), temperature (≥37.7 °C, +1.3), pneumococcal conjugate vaccine (0 doses, +1.2), leukocytosis >15,000 cells/mm^3 or leukopenia <4000 cells/mm^3 (+1.1), neutrophilia >10,000 cells/mm^3 (+1.2), hemoglobin (≥11 g/dL, +2.3), CRP (>100 mg/L, +2.2) (see Figure, Supplemental Digital Content 5, http://links.lww.com/INF/E536). The sum of the weights for each patient was calculated to know the score of each patient. The optimal cutoff point for step 1 to classify a CAP with high sensitivity for bacterial etiology was ≥11 points (sensitivity 93.1%, specificity 57.7%, AUC = 0.80) (Fig. 1). In the external validation, bacteria were classified with a sensitivity 97.3%,

TABLE 1. Variables Included in the Score

Step 1 (viral <11 vs. bacterial >11)	Weight
Age at admission >3 years	10.6
Zero pneumococcal conjugate vaccine doses	1.2
Lack of WoB	2.2
Lack of wheezing	1
Temperature >37.7 °C	1.3
Consolidation on radiograph	5.5
Hemoglobin >11 g/dL	2.3
Leukocytosis >15,000 cells/mm^3 or leukopenia <4000 cells/mm^3	1.1
Neutrophilia >10,000 cells/mm^3	1.2
CRP >100 mg/L	2.2
Step 2 (atypical bacteria <11.7 vs. typical bacteria >11.7)	**Weight**
Age at admission <3 years	6.8
Lack of cough	3.0
Lack of wheezing	5.0
WoB	5.8
Hemoglobin <11 g/dL	5.4
Leukocytosis >15,000 cells/mm^3 or leukopenia <4000 cells/mm^3	2.4
Neutrophilia >10,000 cells/mm^3	3.3

Weight of the values should be added to obtain the total value of the score. Step 1 differentiates viral CAP from bacterial CAP (cutoff point, 11, see Figure 5, Supplemental Digital Content 6, http://links.lww.com/INF/E537, for probabilities of bacterial CAP according punctuation). Step 2 differentiates, among those classified as bacterial CAP, typical bacterial CAP from atypical bacterial CAP (cutoff point, 11.7, see Figure 6, Supplemental Digital Content 8, http://links.lww.com/INF/E539, for probabilities of typical bacterial according punctuation). The result of the scores can be calculated quickly and easily in this online app: https://saradominguez-rodriguez.shinyapps.io/ValsDance_app/ (username: user; password: 0000).

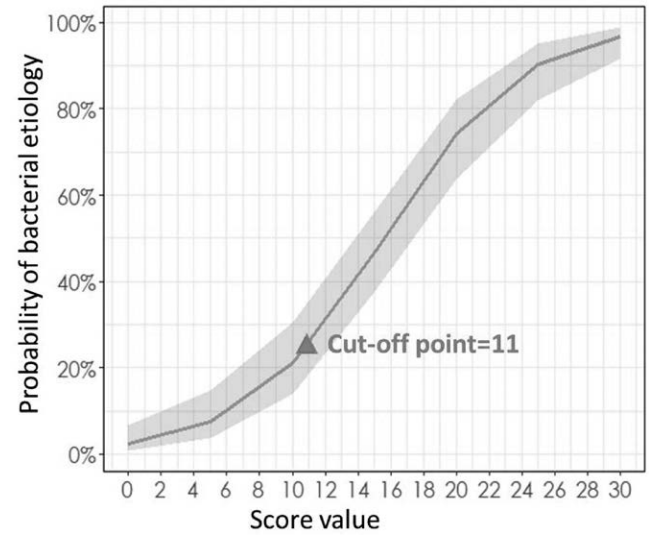

FIGURE 1. Probability of bacterial etiology according to the results of the sum of values of Step 1. A significant risk of having a typical bacterial pneumonia was set on 11. Children with >11 points have >25% risk of bacterial pneumonia and pediatricians should Antibiotics directed against bacterial pneumonia may not be necessary. For an optimal choice of antibiotics, step 2 can be informative (Fig. 2) consider prescription of antibiotics. Below 11 points, the risk of bacterial pneumonia is below 25%. full color online

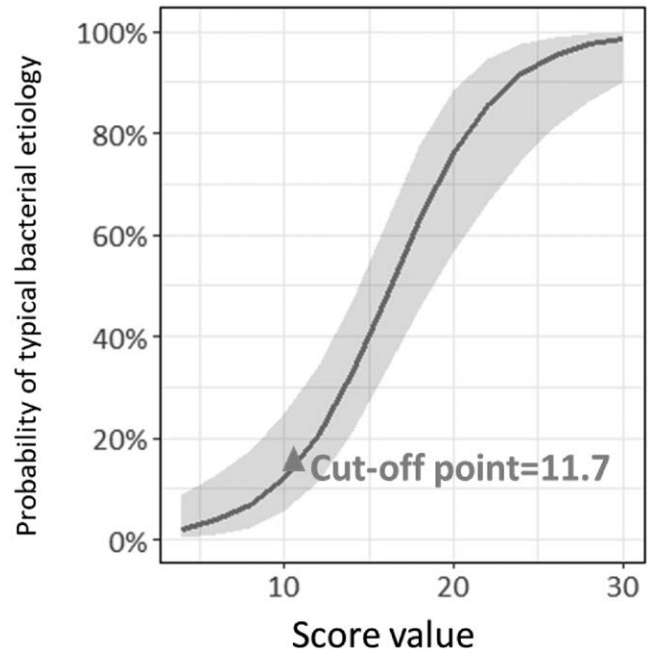

FIGURE 2. Probability of typical bacterial etiology according to the results of the sum of values of step 2. A significant risk of having a typical bacterial pneumonia was set on 11.7. Children with at least 11.7 points have >18% risk of typical bacterial pneumonia and should receive antibiotics specifically directed against typical bacteria. Below 11.7 points, the risk of typical bacterial pneumonia is below 18%. Antibiotics directed against typical bacteria may not be necessary. Antibiotics directed against atypical bacteria might be considered. full color online

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specificity 48.8%, positive predictive value 63.2%, negative predictive value 95.2% and AUC = 0.81 (see Figure, Supplemental Digital Content 6, http://links.lww.com/INF/E537). The positive likelihood ratio was 1.9 (1.40–2.57) and the negative likelihood ratio was 0.06 (0.01–0.39).

Step 2 (Atypical Bacteria vs. Typical Bacteria)

In step 2, participants who scored as bacterial in step 1 were included. According to the multivariable model the step 2 was built with: age at admission (<3 years, +6.8), cough (no, +3), wheezing (no wheezing, +5.0), WoB (yes, +5.8), hemoglobin (<11 g/dL, +5.4), leukocytosis >15,000 cells/mm^3 or leukopenia <4000 cells/mm^3 (+2.4) and neutrophilia >10,000 cells/mm^3 (+3.3). The sum of the weights for each patient was calculated to know the step 2 of each patient. The CRP [OR: 14.5 (3.1–86.9), $P = 0.001$], influenza vaccine [OR: 2.3×10^8 (3.2×10^{-147}-Inf), $P = 0.994$], and radiograph image interpretation [OR: 1.3×10^8 (2.4×10^{-54}-Inf), $P = 0.992$] were excluded in the final model due to their wide confidence interval (see Figure, Supplemental Digital Content 7, http://links.lww.com/INF/E538). The optimal cutoff points for the step 2 to classify a CAP as of typical bacterial etiology was ≥11.7 points (sensitivity 93.3%, specificity 61.4%, AUC = 0.89). Atypical bacteria etiology was classified with <11.7 points (Fig. 2). In the validation, typical bacteria were classified with sensitivity 100%, specificity 64%, positive predictive value 37%, negative predictive value 100% and AUC 0.90 (see Figure, Supplemental Digital Content 8, http://links.lww.com/INF/E539). The positive Likelihood ratio was 2.76 (1.89–4.04) and the negative likelihood ratio 0.0 (-).

The distribution of the patients with identified etiology across the 2 steps is displayed in Fig. 3.

None of the typical bacteria and only 1 of 34 (3%) atypical bacteria scored as viral in the testing set of the step 1. None typical bacteria scored as atypical in the testing set of step 2. Just 4 of 34 (11.8%) atypical bacteria scored as typical in the testing set. Around half of the antibiotics that were used for children with viral CAP would have been saved with this tool.

DISCUSSION

In this study, we propose that most viral, typical bacterial and atypical bacterial CAPs can be differentiated at the time of admission with a score built from easily available clinical, radiographic and analytical parameters. The use of this[1–3] score can be facilitated by an online app. The online app provides probabilities of bacterial infection and, among them, typical or atypical bacterial infection.

Several markers usually considered as common in typical bacterial pneumonia were included in step 2. But 2 features traditionally considered reliable markers of typical pneumonia, consolidation and high CRP, were not included. The reason is that the number of events of "other infiltrates" or low CRP was too sparse to estimate the risk, so the 95% confidence interval was too wide and the certainty was low. Some studies have suggested that procalcitonin has good accuracy for differentiating RSV from *S. pneumoniae* CAP or viral from bacterial CAP.[11–14] PCT and albumin were included in the protocol but were not used in the model due to missing data. Hemoglobin is not a classical marker of differentiation viral/bacterial infection, but inflammation is an important cause of anemia which explains the association of anemia with typical bacteria shown in the step 2.

In previous research, wheezing and CXR with "other infiltrates" have been suggested as predictors of viral CAP,[15] but the distinction between viral and atypical bacteria, and typical from atypical bacteria is not so straightforward, because of significant overlapping.[16,17]

We hypothesize that patients who score below 11 in step 1 may be safely treated without antibiotics, but this needs confirmation in trials. Around half of antibiotics that were used for children with viral CAP had been saved with this tool because neither typical bacteria, nor the most of atypical bacteria, scored as viral in the testing set of the step 1. In addition, no typical bacteria scored as atypical in the testing set of step 2. Only a few atypical bacteria pneumonia scored as typical in the testing set. This is not considered of high relevance since the benefit of antibiotics for *M. pneumoniae* pneumonia is controversial.[18] Some patients with a high score in step 1 had only virus detected. We hypothesize that these patients may have undetected bacterial coinfections. If these

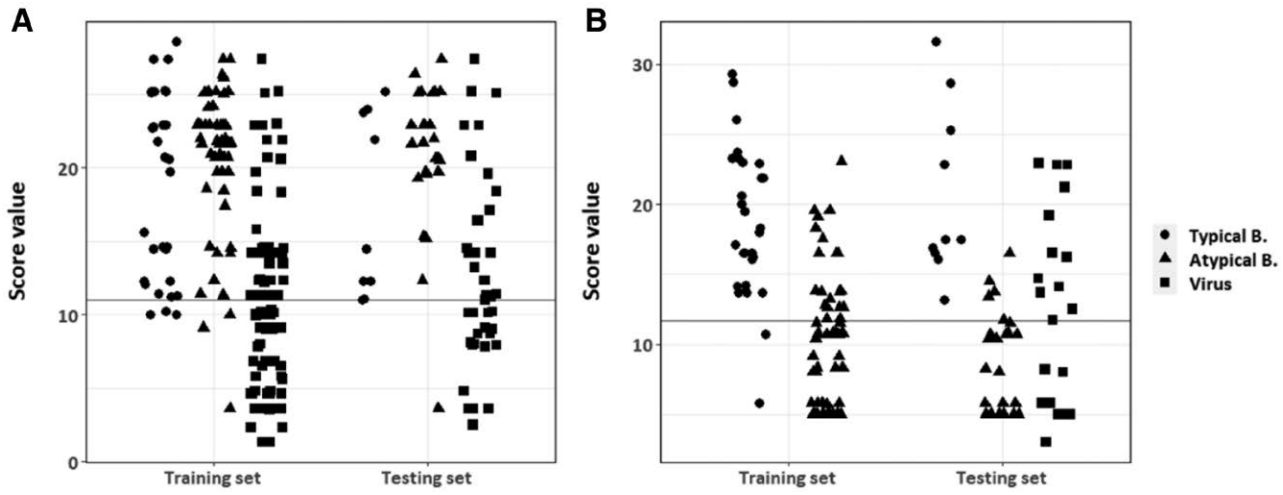

FIGURE 3. Distribution of the sample, according to likely etiologies and results of all patients in step 1 and step 2. A: Step 1, Only 3 of 29 (10.3%) typical bacteria scored as viral, and 2 of 50 (4%) atypical bacteria scored as viral in the training set. No typical bacteria and only 1 of 34 (3%) atypical bacteria scored as viral in the testing set. This patient had PCR positive for *M. pneumoniae* and hMPV in the NPA. No serial serologies were available. B: Step 2, Only 2 of 29 (7%) typical bacteria scored as atypical in the training set. No typical bacteria scored as atypical in the testing set. Four of 34 (12%) atypical bacteria scored as typical in the testing set.

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patients actually had a bacterial infection as expected, the accuracy of the score would be even better than reported.

The value and novelty of this tool are their high predictive values. Some scores tried to achieve the same aim as we did, but the microbiologic standards were less accurate.[19,20] With this tool, we can safely spare a lot of antibiotics routinely used for CAP in children, which may have an impact on the antimicrobial stewardship.

The study has some limitations. One of the main limitations is the low specificity of the scores. We prioritized sensitivity over specificity to avoid misdiagnosis of bacteria in the first step and typical bacterial pneumonia in the second, because CAP caused by typical bacteria are potentially the most severe and are treatable. Therefore, a CAP with ≥25% probability of being caused by typical bacteria is classified by this tool as caused by typical bacteria to prevent false negatives. We considered unacceptable the risk of not treating with antibiotics against typical bacteria a child with ≥25% probability of a serious typical bacterial infection. The well-known and inherent poor sensitivity of the current methods to identify bacterial infections limits the certainty of bacterial attribution. Therefore, we had to compare our scores to imperfect standards. In research where standard is not clear, test accuracy indexes should not be taken as a hard fact. However, the microbiologic approach we used is close to the best available standard in clinical practice.

Another limitation is the lack of a highly reliable standard. The poor sensitivity of the current methods to identify bacterial infections limits the certainty of bacterial attribution. Some patients may have been classified wrongly due to lack of detection secondary to the methods, not to the absence of the pathogen. Same, a positive PCR for viruses may be secondary to residual fragments of nucleic acid or healthy carriage, rather than actual infection. The microbiologic approach we use disclose to the best available standard in clinical practice. Additional methods as cycle threshold analysis and density profile of colonizers agents in NPA by real-time PCR have been used in research, but the use of density to define etiology is controversial, technique-dependent, not validated, and not routinely used.[20] More invasive techniques are not acceptable today, even in research. In the PERCH study, only 37 participants had lung aspirate for microbiologic survey.[5] Bronchoscopy is not warranted for most of the CAP. Again, we had to compare our scores to imperfect standards.

The decision to exclude other viruses such as hRV, ADV, EV, hCoV and hBoV from the viral case definition is controversial. At the time of the design, there was significant literature suggesting that controls have the same proportion of hRV, ADV, EV, hCoV and hBoV than children with pneumonia.[5,9,10] We could have tried to differentiate between colonization and infection by quantitative molecular techniques quantitative and attempt to establish cutoff points. However, this aim was of the scope of this research, and we did not have the capacity to do it. Given the impossibility of distinguishing whether the patients with the aforementioned viruses were carriers alone or if the pneumonia was actually caused by these viruses, we decided to exclude them.

Some patients received antibiotics before arrival, which may have impaired detection of bacteria, and patients with mixed infection may have been labeled as viral CAP. Twenty-one patients with high inflammatory features and only virus detected were labeled as viral, but the score 1 suggested that etiology was bacterial (see Table, Supplemental Digital Content 9, http://links.lww.com/INF/E540). The result was a decrease in the performance of the test because potential bacterial CAPs were classified as viral. If some of those CAPs were actually bacterial, the test performance would be even better. From the individual patient perspective, since viral CAPs would be treated as bacterial (and not the opposite), patients' safety would never be jeopardized.

We acknowledge that the WHO definition for clinical pneumonia does not include radiograph. However, this definition has poor specificity. In settings where radiograph is available, the standard test for diagnosis of pneumonia is the radiograph – although it is imperfect.

Reproducibility of these results should be explored in different settings, especially in areas without routine immunizations for *S. pneumoniae* or where cutoff values for analytical parameters may be different. This analysis was performed before the COVID-19 pandemic. SARS-CoV-2 should be ruled out before using this tool.

CONCLUSIONS

We provide a validated clinical tool to differentiate viral, typical, and atypical CAP safely. This tool can improve the appropriate use of antibiotics in pediatric CAP.

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