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Predictors of Unlikely Bacterial Pneumonia and Adverse Pneumonia Outcome in Children Admitted to a Hospital in Central Vietnam

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Background. Pneumonia is the leading cause of antibiotic use and hospitalization in Vietnam. There is a need for better prediction of unlikely bacterial pneumonia and adverse pneumonia outcome in order to guide hospital admission and improve rational antibiotic use.

Methods. All children under 5 admitted with pneumonia (per clinician assessment) to the Da Nang Hospital for Women and Children were prospectively enrolled. Children were classified as having likely or unlikely bacterial pneumonia and followed for outcome assessment. A Bayesian model averaging approach was used to identify predictors of unlikely bacterial pneumonia and adverse pneumonia outcome, which guided the development of a pragmatic management algorithm.

Results. Of 3817 patients assessed, 2199 (57.6%) met World Health Organization (WHO) pneumonia criteria. In total, 1594 (41.7%) children were classified as having unlikely and 129 (3.4%) as having likely bacterial pneumonia. The remainder (2399; 62.9%) were considered to have disease of uncertain etiology. Factors predictive of unlikely bacterial pneumonia were no fever, no consolidation on chest radiograph, and absolute neutrophil count $<5 \times 10^9$/L at presentation, which had a negative predictive value (NPV) for likely bacterial pneumonia of 99.0%. Among those who met WHO pneumonia criteria, 8.6% (189/2199) experienced an adverse outcome. Not having any WHO danger sign or consolidation on chest radiograph had an NPV of 96.8% for adverse pneumonia outcome.

Conclusions. An algorithm that screens for predictors of likely bacterial pneumonia and adverse pneumonia outcome could reduce unnecessary antibiotic use and hospital admission, but its clinical utility requires validation in a prospective study.

Keywords. childhood; pneumonia; predictor; adverse outcome; antibiotic use.

Pneumonia is a major contributor to childhood mortality, with more than 90% of pneumonia deaths in children aged <5 years occurring in developing countries [1]. Bacterial pneumonia is generally considered to be the main culprit [2], although the establishment of an accurate etiological diagnosis remains a major challenge [3, 4]. Bacterial blood cultures have low yield, while more sensitive polymerase chain reaction–based tests are limited by low sensitivity in blood and poor specificity in respiratory specimens [5]. Viral etiologies may be underestimated in settings with limited diagnostic facilities that adopt syndromic approaches or rely on chest radiograph (CXR) findings. Results from the multicenter Pneumonia Etiology Research for Child Health (PERCH) project found that respiratory syncytial virus (RSV) accounted for >30% of CXR-confirmed pneumonia in children aged <5 years [5].

The use of antibiotics in children with viral pneumonia has come under scrutiny, given global concerns about rising rates of antimicrobial resistance and unnecessary antibiotic use [6]. In Vietnam, as in other East Asian settings, pneumonia is the main driver of pediatric hospitalization and antibiotic use [7, 8]. There is a need for better recognition of bacterial pneumonia in children who are likely to benefit from antibiotic treatment and consideration of rule-out approaches that restrict antibiotic use in those with unlikely bacterial pneumonia. The PERCH study found that elevated C-reactive protein (CRP ≥40 mg/L) was positively associated with confirmed bacterial pneumonia (especially those with *Streptococcus pneumoniae* and *Haemophilus influenzae*) and negatively associated with RSV [9]. A recent study in Vietnam demonstrated that a point-of-care CRP test, using a cutoff of ≥50 mg/L, safely reduced unnecessary antibiotic use in children with an acute respiratory infection presenting to the local primary healthcare centers [10].

Given the limited availability and suboptimal performance of advanced diagnostic tests, the World Health Organization

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(WHO) pneumonia case management approach focuses on basic clinical signs and symptoms [11]. Despite good uptake of this approach and evidence of its value in sub-Saharan Africa and the Indian subcontinent [12], its use remains limited in East Asian countries such as Vietnam [13]. A retrospective analysis of admission data demonstrated that most children admitted with pneumonia in Vietnam did not meet WHO case management criteria, with only a small percentage meeting criteria for severe pneumonia that generally indicate a need for hospital admission [14, 15]. Pediatricians in Vietnam feel uncomfortable with the high bar set for hospital admission by the WHO case management approach, which does not take account of CXR or laboratory findings. In the absence of local data to guide safe practice, most pediatricians prefer to err on the side of caution and adopt observed practice among senior clinicians or perceived practice in developed country settings.

Improving rational antibiotic use and reducing unnecessary hospital admissions, which increases healthcare costs and poses a risk of nosocomial infection, are top priorities for more effective pneumonia case management in Vietnam. Our primary aim in this study was to identify predictors of unlikely bacterial pneumonia among children who present to the hospital with respiratory symptoms, acknowledging that accurate etiological diagnosis is unattainable in a large number of children. We also aimed to identify predictors of an adverse pneumonia outcome and combined the insight gained from predictive models with existing guidance to suggest a potential pragmatic algorithm to reduce unnecessary antibiotic use and hospitalization.

METHODS

We conducted a prospective descriptive study of children aged <5 years admitted with pneumonia over a 1-year period (1 July 2017 to 30 June 2018). The Da Nang Hospital for Women and Children Ethics Committee provided written approval for the study.

Study Setting

The Da Nang Hospital for Women and Children is a provincial referral hospital in central Vietnam, with 150 pediatric beds allocated for respiratory admissions. Severe respiratory infections are usually admitted directly to the intensive care unit (ICU), while nonsevere infections are admitted to the respiratory ward or to a private fee-paying ward (with mild disease only). Patients come directly from home or are referred from district hospitals in Da Nang city and surrounding areas.

Study Population

All children aged 2–59 months admitted to the respiratory ward or ICU with a primary or secondary diagnosis of pneumonia were enrolled. Researchers performed daily recruitment rounds to enroll patients, interview caregivers, and document respiratory signs and symptoms on admission (see Supplementary Material for the data collection form). All data were recorded by research personnel not involved in clinical patient care. Additional clinical, laboratory, and radiological findings, as well as pneumonia outcomes, were finalized and captured on hospital discharge. Children transferred in from district or provincial hospitals were excluded, since the study focused on symptoms and signs documented at hospital presentation. For adverse pneumonia outcome, we excluded children who did not meet revised WHO pneumonia criteria.

Pneumonia Classification and Outcome Definitions

Children were classified as WHO no pneumonia and WHO pneumonia based on revised WHO pneumonia criteria [11]. Table 1 provides a detailed overview of all the relevant definitions and classifications used. For study classification purposes, no pneumonia was defined as WHO no pneumonia plus a normal CXR. Assigned pneumonia etiology was classified based on CRP, with CRP <10 mg/L identifying likely viral pneumonia and CRP ≥50 mg/L identifying likely bacterial pneumonia. All other cases (CRP 10–49 mg/L or CRP not done) were regarded as uncertain. Unlikely bacterial pneumonia was defined as a combination of no pneumonia and likely viral pneumonia. Adverse pneumonia outcome was defined as death or ICU admission in a child with WHO pneumonia on admission.

Data Management and Statistical Analyses

Data were entered into an Epi Data database (V4.4.3.1). Initial data were entered within a day of admission, with final data

Table 1. Overview of Case Definitions Used for Pneumonia, Including Assigned Likely Etiology and Adverse Outcome Definitions

Classification	Definition
WHO case definition	
No pneumonia	Hospital admission with respiratory symptoms, but no tachypnea[a] or chest in-drawing
Pneumonia	
Not severe	Hospital admission with tachypnea[a] or chest in-drawing
Severe	As above plus a danger sign[b]
Assigned likely etiology	
No pneumonia[c]	WHO no pneumonia and a normal chest radiograph
Likely viral pneumonia[c]	WHO pneumonia and CRP <10 mg/L
Likely bacterial pneumonia	WHO pneumonia and CRP ≥50 mg/L
Uncertain	All cases not meeting the definitions above
Adverse pneumonia outcome definition	
Death	Died in hospital
ICU admission	Admitted to ICU at any time during the admission

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; WHO, World Health Organization.

[a]Defined as breath rate of ≥50/min aged 2–11 months or ≥40/min aged 12–59 months [11].

[b]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition.

[c]Combined to constitute those identified as unlikely bacterial pneumonia.

entry and checking completed on hospital discharge. Data were checked for inconsistencies and corrections made by referring to the original patient record. We focused our analyses on children with no pneumonia, likely viral pneumonia, and likely bacterial pneumonia as defined. Children in the uncertain category were excluded from the likely etiology analysis. Relevant clinical and laboratory variables were summarized using descriptive statistics. All statistical analyses were performed using R version 3.5.2 [16].

Factors evaluated included gender, antibiotic use before admission, recent (during the past 2 weeks) admission with an acute respiratory infection, any breastfeeding, cigarette smoke exposure (anyone smoking inside the house), birth weight (low if <2500 g; not included in adverse pneumonia outcome but important consideration for children aged <2 years), any wheeze or runny nose, fever on admission (no if temperature <38.5°C), consolidation on CXR using WHO endpoint criteria for consolidation [17], absolute neutrophil count (low if $<5 \times 10^9$/L), peripheral oxygen saturation (low if SpO_2 <90% in room air), and the presence of WHO danger signs (inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress [grunting or nasal flaring], severe malnutrition) [11]. Wheeze on auscultation was not reliably recorded in all children. For comparative analyses, unrecorded data were regarded as missing values without the use of imputation.

A Bayesian model averaging (BMA) approach was used to search for the most parsimonious predictive model with maximal discriminatory power. Unlike conventional stepwise model-building approaches, which use approximate asymptotic ratio tests to search for a single "best" model, the BMA approach identifies models with the highest posterior probabilities [18]. After selecting the optimal model, its validity was assessed using the Classification And Regression Training (CARET) technique from the CARET package in R [19]. This technique performs internal validation of both the diagnostic and predictive performance of the model. We also assessed the screening value of variables selected by the model by calculating its negative predictive value (NPV) within the study cohort.

RESULTS

In total, 4206 children were hospitalized with pneumonia, as assessed by the admitting physician. Figure 1 provides an overview of participant recruitment. We excluded 1515 children admitted to the private ward, as well as 398 children referred from other hospitals. Of the 3817 pneumonia admissions included in the analysis, 2199 (57.6%) met WHO pneumonia criteria. A CXR was performed in 3606 (94.5%) children, and a CRP was collected in 1076 (28.2%). Among those with a CRP result, 8.0% (305/1076) were classified as likely viral pneumonia and 3.4% (129/1076) as likely bacterial pneumonia based on specified CRP cutoffs. Those without a CRP result or with values between the specified cutoffs (10–49 mg/L) were considered to have disease of uncertain etiology (2399, 62.9%) and excluded from the comparative analysis.

Table 2 presents the CRP results and adverse outcomes documented in children admitted with pneumonia. Among those not meeting WHO pneumonia criteria, 984/1618 (60.8%) had a normal CXR and were classified as no pneumonia. Nearly a third (53/184; 28.5%) of children with WHO severe

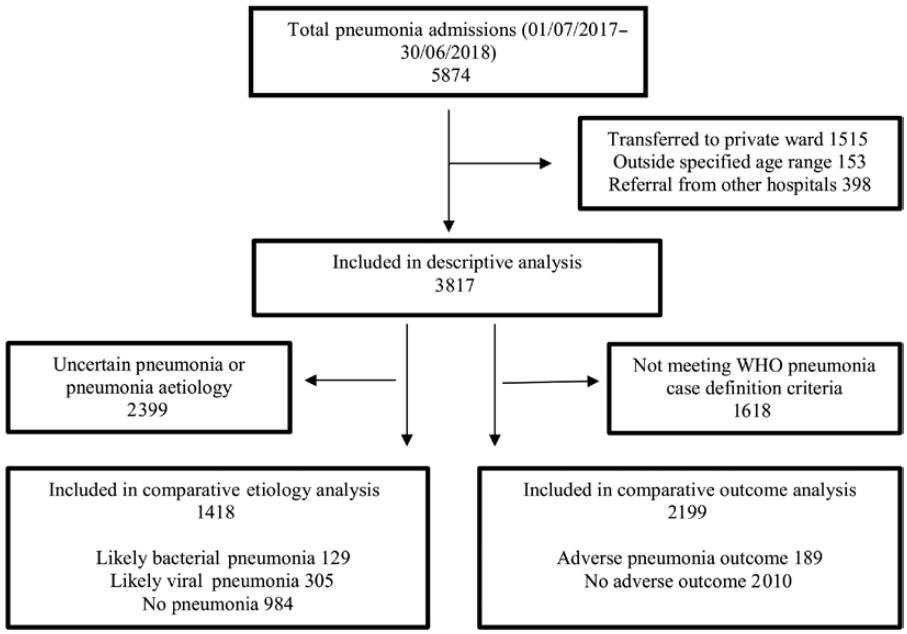

Figure 1. Flow diagram of participant recruitment. Abbreviation: WHO, World Health Organization.

Table 2. Overview of C-Reactive Protein Grading, Used to Assign Likely Etiology, and Adverse Outcome in Different World Health Organization Pneumonia Categories

	WHO No Pneumonia[a]		WHO Pneumonia[a]		Total
	CXR Normal	CXR Abnormal	Not Severe	Severe	n (%)
CRP Grading and Adverse Outcome	n (%)	n (%)	n (%)	n (%)	
CRP grading					
<10 mg/L	**123 (12.5)**	59 (9.3)	**252 (12.5)**	**53 (28.8)**	487 (12.7)
≥50 mg/L	**35 (3.6)**	57 (9.0)	**118 (5.9)**	**11 (6.0)**	221 (5.8)
Other[b]	**826 (83.9)**	518 (81.7)	1645 (81.6)[c]	120 (65.2)[c]	3109 (81.5)
Adverse outcome[a]					
Yes	13 (1.3)	16 (2.5)	**108 (5.4)**	**81 (44.0)**	218 (5.7)
No	971 (98.7)	618 (97.5)	**1907 (94.6)**	**103 (56.0)**	3599 (94.3)
Total	984 (25.8)	634 (16.6)[c]	2015 (52.8)	184 (4.8)	3817

Abbreviations: CRP, C-reactive protein; CXR, chest radiograph; WHO, World Health Organization.

[a]Per definitions provided in Table 1; numbers in bold indicate patient groups included in the comparative analyses.

[b]CRP 10–49 mg/L or unknown.

[c]These cases were excluded from the comparative analysis, since the pneumonia diagnosis or assigned etiology was considered uncertain.

pneumonia had a CRP <10 mg/L, suggestive of a viral infection. Of the children who met WHO pneumonia criteria, 189/2199 (8.6%) experienced an adverse outcome (as defined). A small number of children (13/984; 1.3%) in the no pneumonia group were admitted to the ICU, 10 with bacteremia and a normal CXR and 1 each with severe diarrhea, foreign body aspiration, and severe malnutrition.

Table 3 provides a detailed overview of characteristics associated with unlikely and likely bacterial pneumonia, as well as adverse pneumonia outcome. Boys were overrepresented among children with likely bacterial pneumonia and adverse pneumonia outcome. Pneumococcal vaccination uptake was low overall (approximately 5%) but lowest (2.1%) in those with adverse pneumonia outcome. Cigarette smoke exposure was high (>50%) in all pneumonia categories. SpO_2 was only selectively recorded; therefore, SpO_2 <90% in room air was combined with other WHO danger signs for prediction model analyses.

The best predictive model for unlikely bacterial pneumonia included the following 3 variables: no fever on admission, neutrophil count $<5 \times 10^9$/L, and no consolidation on CXR (Table 4). These predictors independently increased the chance of unlikely bacterial pneumonia by 2.2-, 3.1-, and 15.0-fold, respectively. Figure 2A presents a nomogram for determining the likelihood of unlikely bacterial pneumonia. Its use as a diagnostic tool is not envisioned, since the main purpose of the model was to inform a pragmatic screening approach to rule out likely bacterial pneumonia. Table 5 reflects the NPV of variables identified by the model to screen the study population for likely bacterial pneumonia (NPV, 99.0%).

For adverse pneumonia outcome, the selected model included the following 2 variables: WHO danger signs and consolidation on CXR (Table 4). Some models that included a third variable had slightly better predictive value (Supplementary Table 1), but the 2-variable model was considered more pragmatic and likely to perform consistently across the age range. Figure 2B presents a nomogram for determining the likelihood of adverse pneumonia outcome. Supplementary Table 2 indicates the diagnostic accuracy of selected models for unlikely bacterial pneumonia and adverse pneumonia outcome using the CARET package for internal validation.

Figure 3 presents a pragmatic algorithm that combines study findings, existing WHO guidance, and previous findings from Vietnam that used CRP values to guide rational antibiotic use [10]. If this algorithm had been in place during the study period, hospital admission and antibiotic use would have been averted in 955 (25.0%) cases who presented with wheeze and/or runny nose and no fever or danger signs. An additional 1259 (33.0%) cases with no consolidation on CXR and neutrophil count $<5 \times 10^9$/L (or CRP <10 mg/L) were unlikely to benefit from hospitalization or antibiotic use. Table 6 provides an overview of potential positive and negative impacts associated with algorithm implementation. Some children admitted to the ICU did not meet hospital admission criteria, as specified in the algorithm. Most of these children (19/24; 71.2%) had chest in-drawing in the absence of WHO danger signs, which was attributed to bronchiolitis.

DISCUSSION

This is the first prospective study to comprehensively evaluate all pneumonia admissions at a secondary referral hospital in central Vietnam. It demonstrated unnecessary hospitalizations in a large number of children [14] and supports previous observations that many children with respiratory symptoms in Vietnam receive antibiotics without a strong indication [8, 20, 21]. Clinicians often feel that hospitalization is the safe option. However, for children who do not warrant admission, this only increases their risk of adverse effects related to medical care. It is also hugely disruptive to families and their

Table 3. Characteristics of Children Admitted With Unlikely and Likely Bacterial Pneumonia and Those Who Experienced an Adverse Pneumonia Outcome in Central Vietnam

	Pneumonia Classification,[a] n (%)			
	Unlikely Bacterial			
Characteristic	No Pneumonia	Likely Viral	Likely Bacterial, n (%)	Adverse Outcome[a]
Age, months				
2–11	359 (36.5)	121 (39.7)	31 (24.0)	119 (63.0)
12–23	278 (28.3)	123 (40.3)	73 (56.6)	48 (25.4)
24–59	347 (35.3)	61 (20.0)	25 (19.4)	22 (11.6)
Gender (male)	567 (57.6)	181 (59.3)	83 (64.3)	119 (63.0)
Preadmission antibiotics	472 (48.0)	155 (50.8)	57 (44.2)	67 (35.4)
Recent tuberculosis contact[b]	15 (1.5)	4 (1.3)	5 (3.9)	4 (2.1)
Acute respiratory infection readmission[c]	95 (9.7)	55 (18.0)	22 (17.1)	41 (21.7)
Breastfeeding[d]	913 (92.8)	269 (88.2)	117 (90.7)	160 (84.7)
Pneumococcal vaccination[e]	39 (4.0)	14 (4.6)	8 (6.2)	4 (2.1)
Cigarette smoke exposure[f]	505 (51.3)	151 (49.5)	68 (52.7)	100 (52.9)
Biomass fuel exposure[g]	189 (19.2)	63 (20.7)	23 (17.8)	34 (18.0)
Low birth weight (<2500 g)	56 (5.7)	47 (15.4)	7 (5.4)	41 (21.7)
Preterm (<37 weeks)	78 (7.9)	44 (14.4)	10 (7.8)	41 (21.7)
Day care	497 (50.5)	113 (37.0)	71 (55.0)	27 (14.3)
Any wheeze[h]	160 (16.3)	100 (32.8)	21 (16.3)	67 (35.4)
Runny nose	232 (23.6)	51 (16.7)	20 (15.5)	21 (11.1)
Fever (≥38.5°C)	357 (36.3)	133 (43.6)	80 (62.0)	78 (41.3)
Any World Health Organization danger sign[i]	25 (2.5)	58 (19.0)	14 (10.9)	87 (46.0)
Peripheral oxygen saturation <90%	2/30 (6.7)	28/85 (32.9)	9/27 (33.3)	57/148 (38.5)
Abnormal chest radiograph	0	151 (49.5)	92 (71.3)	130 (68.8)
Consolidation[j]	0	59 (19.3)	61 (47.3)	82 (43.4)
Absolute neutrophil count				
$<5 \times 10^9$/L	447 (45.4)	150 (49.2)	22 (17.1)	75 (39.7)
$\geq 10 \times 10^9$/L	149 (15.1)	38 (12.5)	62 (48.1)	57 (30.2)
Total	984	305	129	189

[a]As defined in Table 1.

[b]Tuberculosis contact within the last 12 months.

[c]Acute respiratory infection readmission within 2 weeks of discharge.

[d]Any breastfeeding.

[e]Child received at least 1 dose.

[f]Anyone smoking inside the house.

[g]Used solid fuel for cooking.

[h]Audible wheeze or wheeze on auscultation.

[i]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition.

[j]Assessed by the lead investigator using World Health Organization endpoint criteria for consolidation [17].

livelihoods, particularly in settings where caretakers have to stay in the hospital with their children. Developing a rational approach to reduce unnecessary hospitalization and antibiotic use is a daunting task, given existing patient expectations, clinicians' risk aversion, profits generated from antibiotic prescriptions, and funding models that sometimes encourage hospitalization [7].

We used our large prospectively collected dataset to develop prediction models for unlikely bacterial pneumonia and adverse pneumonia outcome to assist rational antibiotic use and guide hospital admission strategies. The study focused on children who presented to the hospital, where CXR and blood tests are readily available. The best performing model for unlikely bacterial pneumonia provided reasonable diagnostic accuracy and excellent NPV for likely bacterial pneumonia, providing a good indication of when antibiotics are not required. The emphasis here is different from the standard WHO case management approach [11], which focuses mainly on pneumonia death reduction in resource-limited settings with restricted antibiotic access. East Asia presents a unique challenge given that healthcare access is generally good, antibiotic use unrestricted, and pneumonia death rates low.

Given excessive antibiotic use and increasing antimicrobial resistance in Asian countries [7, 10], we aimed to identify children unlikely to benefit from antibiotics. Previous prediction studies identified temperature on admission ≥39°C, neutrophil count $\geq 8 \times 10^9$/L (bands ≥5%), and an abnormal CXR as risk factors for bacterial pneumonia [22, 23]. Consolidation on CXR

Table 4. Selected Predictive Models for Unlikely Bacterial Pneumonia and Adverse Pneumonia Outcome Identified by the Bayesian Model Averaging Approach

Independent Predictor	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value	Area Under the Receiver Operating Characteristic Curve
Unlikely bacterial pneumonia			
No fever on admission (<38.5°C)	2.2 (1.4–3.3)	<.001	0.80
Neutrophil count < 5×10^9/L	3.1 (1.9–5.2)	<.001	…
No consolidation on chest radiograph	15.0 (9.6–23.4)	<.001	…
Adverse pneumonia outcome			
Consolidation on chest radiograph	4.4 (3.1–6.2)	<.001	0.79
Any World Health Organization danger sign[a]	11.6 (8.2–16.5)	<.001	…

[a]Including peripheral oxygen saturation <90% in room air, respiratory distress (grunting or nasal flaring), inability to drink or breastfeed, vomiting everything, lethargy or convulsions, severe malnutrition.

has shown consistent value between studies [17, 24], although it is not considered specific for bacterial infection [12]. Vietnam is an exemplar of an Asian country in transition to low child mortality [13], with relatively low risk for bacterial pneumonia [25] and an increased need to reduce unnecessary antibiotic use and hospitalizations [14]. Our findings relate only to children

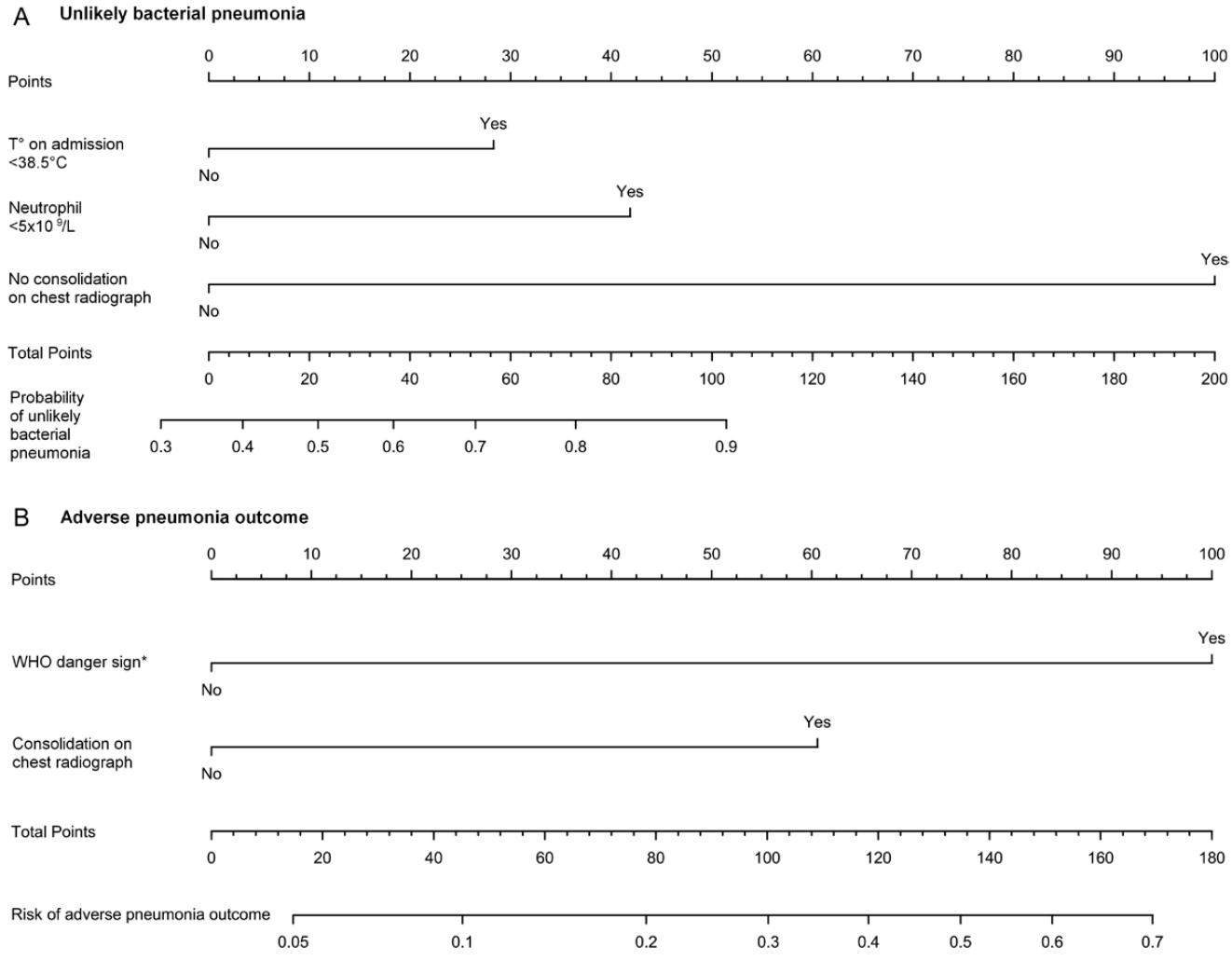

Figure 2. Nomogram for predicting unlikely bacterial pneumonia and adverse outcome. *Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition, and peripheral oxygen saturation < 90% in room air (when documented). Instructions for use: Sum the points awarded to each specified predictor and plot the final sum on the Total Points axis; draw a vertical line down to the risk bar below to find the individual's probability of having the particular outcome. However, its use as a diagnostic tool is not envisioned. Abbreviations: SpO_2, peripheral oxygen saturation; WHO, World Health Organization.

Table 5. Screening Value of Variables Identified by the Bayesian Model Averaging Approach to Rule Out Likely Bacterial Pneumonia and Adverse Pneumonia Outcome

	Likely Bacterial Pneumonia[a]	Adverse Pneumonia Outcome[a]
Screening Value	Fever on Presentation,[b] Consolidation on CXR[c] *or* Neutrophil Count ≥5 × 10^9/L	World Health Organization Danger Sign[d] *or* Consolidation on CXR[c]
Sensitivity	96.9%	72.0%
Specificity	30.3%	80.5%
Positive predictive value	12.2%	25.8%
Negative predictive value	99.0%	96.8%
Without considering fever on presentation[b]	Consolidation on CXR[c] or neutrophil count ≥5 × 10^9/L	
Sensitivity	89.1%	…
Specificity	45.0%	…
Positive predictive value	14.0%	…
Negative predictive value	97.6%	…

Abbreviation: CXR, chest radiograph.

[a]As defined in Table 1.

[b]Temperature on admission ≥38.5°C.

[c]Assessed by the lead investigator using World Health Organization endpoint criteria for consolidation [17].

[d]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition, and peripheral oxygen saturation < 90% in room air.

who present to hospital emergency departments with ready access to CXR and first-line blood tests. WHO guidelines should be applied to children who present to community clinics, for which they were primarily developed [11].

Wheeze has been associated with viral infections in both African [26] and Asian settings [27]. However, although children with likely viral pneumonia wheezed twice as frequently as those with likely bacterial pneumonia, it was not selected by the BMA approach. This may have been affected by the fact that the presence or absence of wheeze on auscultation was not documented in about one-third of children on admission. Revised WHO guidance recommends that a child with wheeze and no fever, in the absence of any danger sign, should not receive an antibiotic [28]. However, if an initial clinical determination is not possible, a CXR and full blood count (and/or CRP) could provide clinicians with additional confidence to withhold antibiotics in a child with respiratory symptoms.

We also focused on factors that predict adverse pneumonia outcome, which identified the presence of WHO danger signs and consolidation on CXR as the strongest predictors. The WHO case management approach utilizes the presence of WHO danger signs to guide hospitalization. However, in hospital-based settings with adequate resources, consolidation on CXR provides clinicians with another important line of information. Despite the good NPV of WHO danger signs or consolidation on CXR for adverse pneumonia outcome, it is difficult to be too

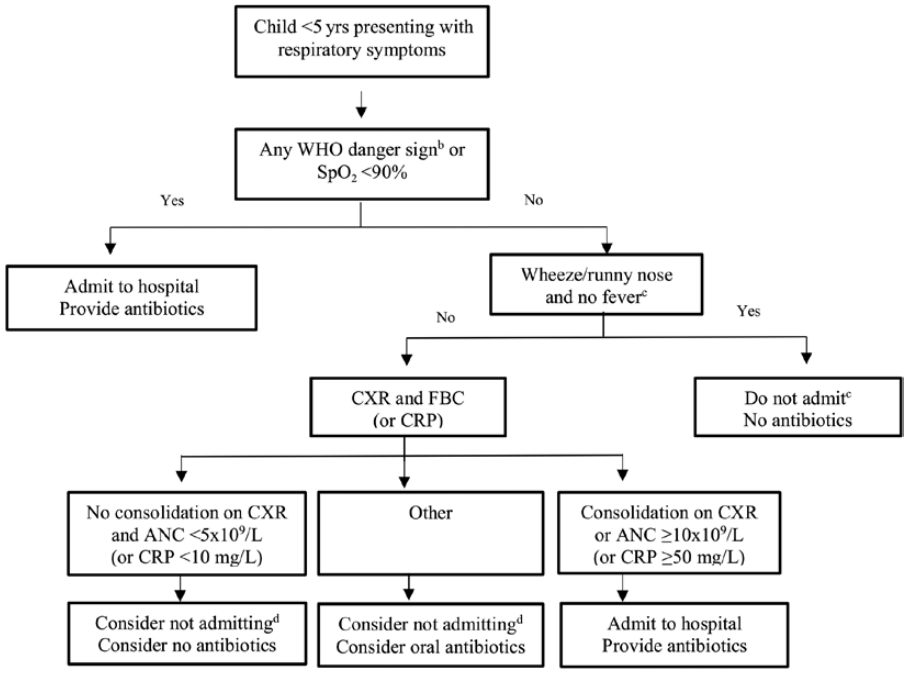

Figure 3. Proposed pragmatic algorithm[a] to guide rational antibiotic use and hospitalization in children who present to the hospital with respiratory symptoms. Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; CXR, chest radiograph; FBC, full blood count; SpO_2, peripheral oxygen saturation; WHO, World Health Organization. [a]Incorporating study findings, existing WHO guidance, and previous findings from Vietnam that used CRP values to guide rational antibiotic use [10]. [b]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition. [c]As per WHO recommendation [28]. [d]Admit and consider antibiotics if any deterioration or relevant clinical concern.

Table 6. Potential Positive and Negative Impacts If the Suggested Algorithm[a] Was Implemented

Impacts Resulting from Algorithm Use (N = 3817)	N (%)
Potential positive impact	
Hospitalization and antibiotic use avoided	955 (25.0)
Chest radiograph avoided	955 (25.0)
Hospitalization reconsidered	1259 (33.0)
Antibiotic use reconsidered	2191 (57.4)
Potential negative impact	
Intensive care unit admissions that might have been sent home	24 (0.7)
Chest in-drawing without World Health Organization danger signs	19/24 (71.2)
Nosocomial infection	3/24 (12.5)
Congenital heart disease	2/24 (8.3)
Presumed sepsis	1/24 (4.0)
Foreign body	1/24 (4.0)

[a]Algorithm as presented in Figure 3.

prescriptive given the variety of clinical syndromes with which children present to the hospital, including asthma, foreign body aspiration, and sepsis. However, our data show that adoption of a simple, pragmatic approach could greatly reduce unnecessary hospital admissions.

The Respiratory Index of Severity in Children was developed in South Africa [26]; however, its translatability to Asian settings is limited by increased rates of hospitalization [14], wheezy pneumonia [14, 27], and preadmission antibiotic use [10, 14], while rates of human immunodeficiency virus (HIV) infection and death are greatly reduced compared to African countries [1]. Our study identified WHO danger signs or SpO_2 <90% in room air as an important predictor of adverse outcome. Although hypoxemia is not included among traditional WHO danger signs [11], the use of pulse oximetry in combination with integrated management of childhood illness has been found to be highly cost effective [29]. Unfortunately pulse oximetry is not universally available and was only recorded in 10% of patients in our study, but we believe it is an important factor that should be grouped with WHO danger signs [14].

Study strengths include the prospective study design and rigorous analytical approach. While conventional stepwise approaches focus mainly on the strengths of association between selected predictors and the outcome to identify a single "best" model, the BMA approach considers all potential models, which substantially improves its predictive performance [30]. In addition, internal model validation was performed using the CARET technique. Study limitations include the fact that children with uncertain pneumonia, which represented the largest group, were excluded from the analysis. However, focusing on those with a certain diagnosis facilitated detection of the most reliable predictive signal, which should apply to the whole study cohort. Few children had comorbid conditions such as HIV coinfection or severe malnutrition, although this is broadly representative of the situation in East Asia. We could only assess likely etiology in the absence of microbiological confirmation, but this is a major challenge in all pneumonia research [4, 12, 13]. We acknowledge that likely bacterial pneumonia (as defined) may have excluded children with atypical pneumonia or tuberculosis, but infections with atypical pathogens are relatively uncommon in children aged <5 years [31], while a history of recent tuberculosis exposure or typical CXR findings [32], should direct a tuberculosis diagnosis. Any proposed algorithm will have to be augmented by basic clinical acumen.

CONCLUSIONS

Identifying accurate predictors of unlikely bacterial pneumonia and adverse pneumonia outcome in children who present to hospital with respiratory symptoms may reduce unnecessary antibiotic use and hospital admission. Based on our study findings and existing guidance, we propose a pragmatic management algorithm to improve rational decision making, which requires validation in a prospective study to confirm its clinical utility and assess potential risks.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. T. K. N., S. M. G., and B. J. M. conceptualized the study and designed the protocol. P. T. K. N. collected the data and drafted the manuscript. P. T. K. N., B. J. M., and T. S. T. analyzed the data. All authors reviewed and approved the final manuscript.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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