ARTICLE COVERSHEET

LWW_CONDENSED(7.75X10.75)

SERVER-BASED

Article : PEC50667
Creator : dpc_lww
Date : Thursday May 4th 2017
Time : 13:52:06
Number of Pages (including this page) : 11

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

ORIGINAL ARTICLE

Assessing Severity in Pediatric Pneumonia
Predictors of the Need for Major Medical Interventions

AQ1 *Are Stuwitz Berg, MD,*† Christopher Inchley, MBChB, PhD,* Hans Olav Fjaerli, MD, PhD,* Truls Michael Leegaard, MD, PhD,†‡ and Britt Nakstad, MD, PhD*‡*

Objective: The aim of this study was to determine potential predictors of the need for major medical interventions in the context of assessing severity in pediatric pneumonia.

Methods: This was a prospective, cohort study of previously healthy children and adolescents younger than 18 years presenting to the pediatric emergency room with clinically suspected pneumonia and examining both the full cohort and those with radiologically confirmed pneumonia. The presence of hypoxemia (peripheral oxygen saturation ≤92%), age-specific tachypnea, high temperature (≥38.5°C), chest retraction score, modified Pediatric Early Warning Score, age, C-reactive protein, white blood cell (WBC) count, and chest radiograph findings at first assessment were analyzed by univariate and multivariate analyses to examine their predictive ability for the need for major medical interventions: supplemental oxygen, supplemental fluid, respiratory support, intensive care, or treatment for complications during admission.

Results: Fifty percent of the 394 cases of suspected pneumonia and 60% of the 265 cases of proven pneumonia were in need of 1 or more medical interventions. In multivariate logistic regression, only the presence of hypoxemia (odds ratios, 3.66 and 3.83 in suspected and proven pneumonia, respectively) and chest retraction score (odds ratios, 1.21 and 1.31, respectively for each 1-point increase in the score) significantly predicted the need for major medical interventions in both suspected and proven pneumonia. Specificity of 94% or greater, positive likelihood ratio of 6.4 or greater, and sensitivity of less than 40% were found for both hypoxemia and chest retraction score in predicting major medical interventions. C-reactive protein and white blood cell count were not associated with the need for these interventions, whereas multifocal radiographic changes were.

Conclusions: Hypoxemia and an assessment of chest retractions were the predictors significantly able to rule in more severe pneumonia, but with a limited clinical utility given their poor ability to rule out the need for major medical interventions. Future validation of these findings is needed.

Key Words: pneumonia, sensitivity and specificity, severity predictors

(*Pediatr Emer Care* 2017;00: 00–00)

Respiratory tract infections including community-acquired pneumonia (CAP) are a common reason for seeking medical attention and hospitalization in childhood.[1,2] One of the most important decisions in the management of acute lower respiratory tract infection (ALRI) in childhood is whether to treat the child ambulatory or admit for hospital-based care. An initial assessment of severity is important to correctly determine the adequate site of care.[3] Literature documenting predictors of severity and hospitalization in pediatric pneumonia is up until now sparse, especially for resource-rich areas, and a validated scoring system to identify children in need of hospitalization has been solicited by current guidelines.[4] As a reply to this, a large prospective US multicenter study recently published one of the first prognostic models for predicting severity in pediatric pneumonia, as defined by clinical outcome.[5] In line with this, an assessment of the likelihood of major medical interventions may be the most feasible method for determining the need for hospitalization. Such an initial assessment will influence microbiological investigations performed, treatment given including antibiotics, and length of treatment. A recent review on the management of severe CAP highlights the differences in severity assessment in resource-poor versus resource-rich areas in the world.[6] Systematic reviews have focused on predictors in serious infection in general.[7,8] Up until the previously mentioned prospective US study, most observational studies the last decades focused on the diagnosis of pneumonia,[9–12] and the few assessing predictors of severity either consider respiratory infections in general,[13] other respiratory infections than pneumonia,[14] or only radiographic changes.[15,16] We have recently published results demonstrating an increasing proportion of viral and subsequent decrease in bacterial pneumonia in our cohort,[17] in line with other pneumonia etiology studies after implementation of routine infantile pneumococcal immunization.[18,19] This change in etiology may influence clinical presentation and the distribution of potential predictors of the need for major medical interventions in pediatric CAP. In this study, we consider factors readily available in pediatric emergency departments in resource-rich settings: symptoms, clinical signs, chest radiography, and inflammatory markers.

The primary objective was to prospectively study potential predictors of the need for major medical interventions of suspected and radiologically proven pneumonia, in previously healthy children and adolescents in a population with high pneumococcal conjugate vaccine coverage. Secondarily, we assessed etiology in relation to this need.

MATERIALS AND METHODS

Study Design, Population, and Ethics

This prospective, observational cohort study was conducted at the Department of Pediatric and Adolescent Medicine, Akershus University Hospital, Norway, from January 1, 2012, until January 1, 2014. All previously healthy patients younger than 18 years presenting to the pediatric emergency department with signs of ALRI (fever or history of fever and 1 or more signs of ALRI: tachypnea, chest retractions, cough) and where radiography was taken because of suspected pneumonia were considered for inclusion. Both ambulatory-treated patients and those in need

From the Departments of *Pediatric and Adolescent Medicine and †Microbiology and Infection Control, Akershus University Hospital; and ‡Institute of Clinical Medicine, Faculty of medicine, University of Oslo, Norway.
Disclosure: The authors declare no conflict of interest.
Reprints: Are Stuwitz Berg, MD, Department of Pediatric and Adolescent Medicine, Akershus University Hospital, Postal Box 1000, 1478 Lørenskog, Norway (e-mail: arebe@medisin.uio).
A.S.B. received research grants from Akershus University Hospital and South-Eastern Norway Regional Health Authority. The study received grants for running expenses from the Grimsgaard Foundation and the Norwegian Organization for Surveillance of Antimicrobial Resistance. These sponsor had no part in conducting the study, and all researchers were independent of the sponsors.
Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 0749-5161

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

of hospitalization were eligible for inclusion. Chest radiography and diagnostic tests were taken at inclusion, and medical history and clinical findings were recorded on a standardized chart. All treatment was given at the clinician's discretion according to hospital guidelines and was retrieved from the hospital's electronic patient journal system. Patients with current infection acquired abroad or in hospital and children with a chronic disease that predisposes to respiratory tract infection were excluded (severe motor impairment, innate or iatrogenic immunodeficiency, cystic fibrosis, or other chronic disease that predisposes to pneumonia). Presentation with wheeze or a history of asthma was not a criterion for exclusion. Guardians or patients older than 16 years signed a written informed consent. The Regional Ethics Committee and the local Data Protection Officer approved the study.

Clinical Features

Clinical features that could potentially predict the need for a major medical intervention chosen in the present study were in line with clinical symptoms and signs included in the severity assessment of the British Thoracic Society's Guidelines on management of pneumonia,[3] which also overlaps with the severity assessment of the World Health Organization.[20] Data on predictors were collected by the nurse and/or the attending physician in the pediatric emergency room at first assessment: (1) hypoxemia (categorical) defined as peripheral oxygen saturation (Spo_2) of 92% or less measured by pulse oximetry (Dash 5000 patient monitor; GE Healthcare); (2) chest retraction score (continuous) from the Respiratory Distress Assessment Instrument with assessment of supraclavicular, intercostal, and subcostal retractions (1 point for mild, 2 for moderate, and 3 points for marked retractions, maximum 9 points)[21]; (3) age-specific tachypnea (categorical) counted for 1 full minute: younger than 1 month, more than 70 breaths/min; younger than 1 year, more than 50 breaths/min; younger than 3 years, more than 40 breaths/min; older than 3 years, more than 30 breaths/min.[22]; (4) modified Pediatric Early Warning Score (PEWS, continuous) as previously described[23]; (5) temperature 38.5°C or greater, either measured (Bosotherm Basic rectal thermometer [Bosch and Son, Germany] or Genius2 tympanic thermometer [~~Covidien, Mass~~]) or a recent history of fever (to reduce the impact of previous antipyretic treatment); and (6) age in years. Assessment of clinical features was performed before receiving major medical interventions except where this was clinically not feasible (eg, circulatory-compromised children in need of fluid resuscitation, children treated by paramedics under transport).

AQ2 AQ3

Laboratory Tests and Classification of Cases

Radiologically proven pneumonia was defined as cases in which 2 pediatric radiologists independently and blinded for clinical data found localized or interstitial infiltrates consistent with pneumonia.[17] Perihilar changes alone were not considered as pneumonia.[24] Localized infiltrates found in 2 or more separate locations (either unilaterally or bilaterally) were categorized as multifocal, and complications (parapneumonic effusion, necrotizing pneumonia) were noted.

As previously published, an extensive microbiological diagnostic workup was performed.[17] In brief, the microbiological workup consisted of (1) bacterial culture from blood (obtained in 83% of suspected CAP cases) and from pleural fluid (obtained in all 7 patients where pleural tapping was clinically indicated); (2) paired sera (obtained in 77% of suspected CAP cases) examined for serological evidence of recent infection with respiratory syncytial virus A/B, influenza virus A/B, parainfluenza virus 1–3, adenovirus (all complement fixation tests), *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Streptococcus pneumoniae* (enzyme-linked immunosorbent assay for immunoglobulin G against pneumolysin and the novel flow cytometric analysis of binding of serum antibodies to live pneumococci); and (3) molecular diagnostic tests (polymerase chain reaction) of nasopharyngeal specimens (obtained in 97% of suspected CAP cases) tested for respiratory syncytial virus A/B, parainfluenza virus 1–4, influenza virus A/B, human metapneumovirus, rhinovirus/enterovirus, human bocavirus, adenovirus, *M. pneumoniae*, and *C. pneumoniae* (interpretation of viral polymerase chain reaction findings were obtained with a strict cycle threshold cutoff of 35 to diminish false-positive results). According to these tests, cases were categorized into (1) viral infection without evidence of bacterial coinfection, (2) atypical bacterial infection (*M. pneumoniae* and/or *C. pneumoniae*) with or without viral coinfection, or (3) other bacterial infection (predominantly *S. pneumoniae*) with or without viral coinfection.

Blood for C-reactive protein (CRP) (in mg/L) and white blood cell (WBC) count ($\times 10^9$/L), including differential count, were taken on enrolment.

Definition of Outcome

Major medical interventions included in this study were as follows: (1) supplemental oxygen requirement, which according to hospital guidelines is given if Spo_2 is 92% or less for more than 2 hours or Spo_2 is 88% or less at any time; (2) supplemental fluid requirement, intravenously or through nasogastric tube; (3) need for respiratory support (continuous positive airway pressure or respirator); (4) transfer to an intensive care unit (respiratory failure, impaired circulation, etc); and (5) treatment for complicated pneumonia (parapneumonic effusion requiring chest drain, necrotizing pneumonia, and others).

Statistical Analysis

Statistical analyses were calculated using IBM SPSS Statistics version 22. Significance levels were 2-sided and set at $P < 0.05$. Continuous data were skewed and therefore presented as median with interquartile range (IQR) and analyzed with Mann-Whitney *U* test/Kruskal-Wallis test. Categorical data were analyzed with χ^2 test. Cases with missing data were excluded from the analyses. Receiver operating characteristic curves were used to examine the discriminatory performance of the continuous variables CRP and WBC count in the dichotomous outcome needing 1 or more major medical interventions versus not needing such interventions. Logistic regression was performed to assess the ability of the 6 potential clinical predictors described previously to predict the outcome needing 1 or more major medical interventions versus not needing such interventions. A simultaneous entry approach was used prior to a stepwise approach. Interaction was assessed between age and all other variables and reported if found. AQ4

RESULTS

Cases

We included 394 cases of ALRI with chest radiography taken because of suspected CAP, of which 265 cases (67.3%) had radiologically confirmed CAP (Fig. 1). Of the 129 cases (32.7%) of suspected pneumonia without radiographic evidence of pneumonia, 82 cases (63.6%) were deemed to have a normal chest radiograph, 42 (32.6%) only perihilar involvement, and 5 cases (3.9%) had other findings. Fifty-nine (45.7%) of those without radiographic evidence of pneumonia had a discharge diagnosis F1

© 2017 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

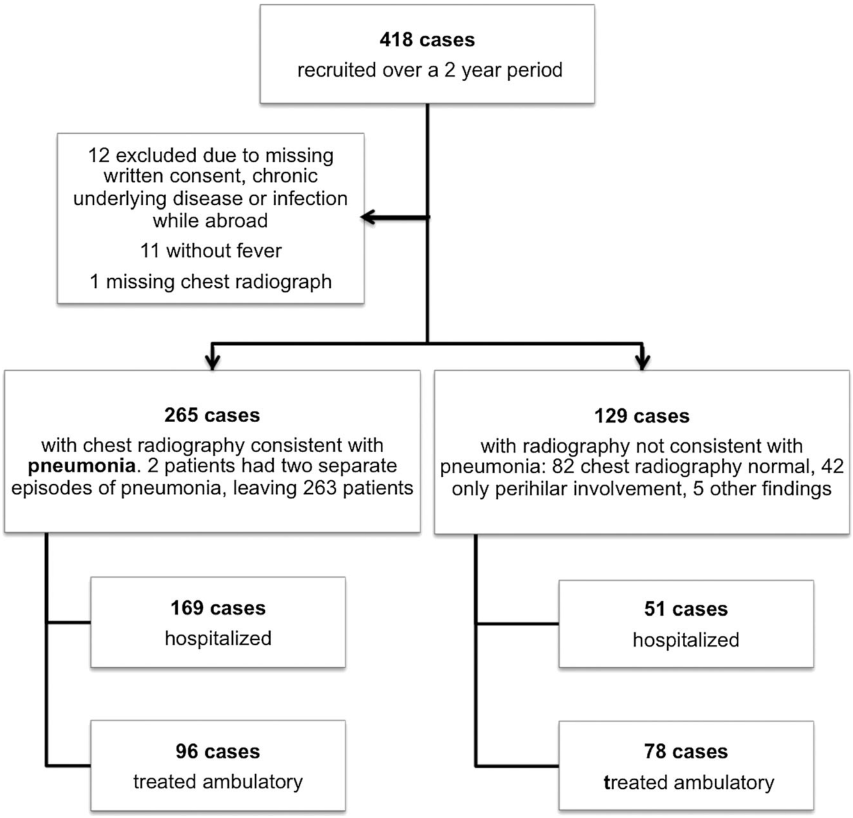

FIGURE 1. Patient inclusion.

of pneumonia (not counted as pneumonia cases), whereas the rest received a diagnosis of bronchiolitis (21 [16.3%]) or other respiratory tract infections (49 [38%]) on discharge. Three hundred forty (86.3%) of all included cases had received 1 or more doses of pneumococcal conjugate vaccine.

Of the 394 suspected cases, 195 cases (49.5%) were treated with 1 or more of the major medical interventions, whereas this was received by 159 (60%) of the 265 CAP cases. Demographics, clinical features, inflammatory markers, radiological findings, and antibiotic treatment at baseline by severity are presented in
T1 T2 Tables 1 and 2. The number of patients who received the different major medical interventions in the full cohort (with number of cases in the 265 CAP cases in parentheses): 20 (19) treated with continuous positive airway pressure, 5 (4) were intubated and on respirator, 7 (7) were treated with a chest drain, 9 (8) were moved to an intensive care unit, 122 (103) received supplementary oxygen, and 146 (123) received supplementary fluid. If the need for supplemental fluids was excluded, 128 cases (32.5%) were treated with 1 or more of the major medical interventions of the 394 suspected cases and 108 (40.8%) of the 265 proven CAP cases.

Clinical Features and the Need for Major Medical Interventions

In the univariate analyses (Tables 1 and 2), all 6 potential clinical severity predictors except high temperature were significantly associated with the need for major medical interventions. The multivariate logistic regression model for the outcome needing 1 or more major medical interventions compared with not needing such a treatment was significant ($P < 0.0001$) in both suspected and proven pneumonia, with a C-statistic of 0.76 (95% confidence interval [CI], 0.70–0.81) for suspected pneumonia and 0.79 (95% CI, 0.73–0.83) for radiologically proven pneumonia. The presence of hypoxemia, chest retraction score, and PEWS provided unique statistically significant contributions to the model when analyzing all 394 suspected cases, whereas for the 265 proven CAP cases, this was the case for the presence of hypoxemia and the chest retraction score (Table 3). A T3
significant interaction was found in both groups between age and chest retraction score, and in age-stratified analyses (<2, 2–5, and >5 years), the significant predictive ability of the chest retraction score remained in the 2 youngest-age groups.

Logistic regression analyses were repeated after excluding supplemental fluid requirement from the major medical interventions. Statistical models remained significant ($P < 0.0001$) for both suspected and proven CAP, and whereas PEWS lost unique significance, the presence of hypoxemia and the chest retraction score provided even higher odds ratios (ORs) (presence of hypoxemia: OR of 5.00 [95% CI, 2.63–9.53] for suspected and OR of 6.26 [95% CI, 2.81–13.96] for proven CAP; chest retraction score: OR of 1.39 [95% CI, 1.21–1.61] for suspected and OR of 1.51 [95% CI, 1.25–1.83] for proven CAP).

Table 4 presents sensitivity, specificity, and likelihood ratios T4
of the clinical variables with unique significant predictive ability in the multivariate analyses, alone and in combination.

Inflammatory Markers and the Need for Major Medical Interventions

In univariate analyses, higher CRP values were associated with the need for 1 or more major medical interventions in suspected but not in proven CAP. White blood cell count was not associated with this need (Tables 1 and 2). Receiver operating characteristic curves for the ability of CRP values and

© 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1. Demographics, Clinical Features, Inflammatory Markers, Radiological Findings, and Antibiotic Treatment at Baseline in 394 Cases of ALRI With Suspected Pneumonia, by the Need for Major Medical Intervention (MMI)

	Needing MMI (n = 195)	Not Needing MMI (n = 199)	*P**
Age, median (IQR), y	1.7 (1.0–2.6)	2.3 (1.4–4.0)	<0.001†
Male sex	102 (52.3%)	118 (59.3%)	0.16
Hospitalized	195 (100%)	31 (15.6%)	<0.001
Days sick on inclusion, median (IQR)	3 (2–5)	4 (2–6)	0.15†
Temperature ≥38.5°C	154 (79.0%)	156 (78.4%)	0.32
Presence of hypoxemia (Spo_2 ≤92%)	73 (37.4%)	11 (5.5%)	<0.001
Tachypnea present	172 (88.2%)	118 (59.3%)	<0.001
Chest retraction score, median (IQR)	2 (0–5)	0 (0–1)	<0.001
Chest retraction score ≥6	40 (13.6%)	5 (2.5%)	<0.001
PEWS, median (IQR)	4 (2.25–5)	3 (1–4)	<0.001†
PEWS ≥3	138 (70.8%)	75 (38.5%)	<0.001
Laboratory findings			
CRP, median (IQR), mg/L	80 (31–170)	50 (18–150)	0.008†
WBC count, median (IQR), $\times 10^9$/L	11.8 (9.3–17.9)	11.7 (8.4–16.0)	0.25†
Radiological findings			
Consolidation	159 (81.5%)	106 (53.3%)	<0.001
Multifocal changes	99 (50.7%)	48 (24.1%)	<0.001
Interstitial changes	2 (1.0%)	2 (1.0%)	0.98
Pleural fluid	8 (4.1%)	7 (3.5%)	0.75
Treatment			
No antibiotics given	57 (29.2%)	69 (34.7%)	0.28
Treated with full-course antibiotics‡	106 (54.4%)	99 (49.8%)	0.60

All numbers given as n (% of total in each column), unless were otherwise indicated. Missing data in fewer than 10 cases in all variables with the exception of PEWS (missing data in 70 cases).

*All significance levels are 2-sided, and all analyses are χ^2 test, except where indicated.

†Mann-Whitney *U* test.

‡A minimum of 5 days was regarded as full course for all antibiotics except azithromycin, for which 3 days was regarded as a full course.

WBC count to discriminate the need for major medical interventions from no need provided poor areas under the curve (<0.60) in both the suspected and proven cases. Given the results of the receiver operating characteristic curves, no attempt to provide test characteristics for either of the inflammatory markers was done.

Radiological Findings and the Need for Major Medical Interventions

The presence of a localized consolidation was significantly associated with the need for major medical intervention in the 394 cases of suspected pneumonia (Table 1). Furthermore, multifocal changes were significantly associated with this need in both the 394 suspected cases and the 265 proven CAP cases (Tables 1 and 2). Test characteristics for these radiological findings alone and in combination with clinical findings are presented in Table 4. Fifteen cases (5.7%) of parapneumonic effusion were found, but only 7 (2.6%) of these were found to require chest drainage. No other complications were found.

Etiology and the Need for Major Medical Interventions

A pathogen was detected in 223 (84.2%) of the 265 CAP cases, with only viral infections in 168 (63.4%), atypical bacteria in 21 (7.9%) (predominantly *Mycoplasma*, 5% only atypical bacterial and 3% mixed with virus), and other bacteria in 34 (12.8%) (predominantly *Pneumococcus*, 4% only bacterial and 9% mixed with virus).[17] As seen in Table 5, atypical etiology was significantly associated with not needing a major medical intervention in both suspected and proven pneumonia, but when stratified by age (<2, 2–5, and >5 years), no significant association between viral, atypical, or bacterial etiology and needing a major medical intervention was found. T5

DISCUSSION

We studied potential predictors, readily available at first assessment, of the need for 1 or more major medical interventions in cases of suspected and proven pneumonia. Risk factor assessment for major medical interventions may be a practical approach when assessing severity and the need for hospitalization. In 394 cases of suspected CAP and then in the 265 radiography-proven cases, the presence of hypoxemia and the degree of chest retractions were the 2 clinical features consistently predicting the need for major medical interventions in both univariate and multivariate analyses. Because receiving supplemental oxygen was the second most common major medical intervention, the predictive ability of hypoxemia at inclusion was expected. Also, the predictive ability of the chest retraction score was expected, but that other factors and perhaps especially tachypnea failed to predict severity was a more surprising finding. With high specificity and positive likelihood ratios, these 2 clinical features are good at ruling in the need for major medical interventions. On the other

© 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 2. Demographics, Clinical Features, Inflammatory Markers, Radiological Findings, and Antibiotic Treatment at Baseline in 265 Patients With Radiologically Confirmed Pneumonia, by the Need for Major Medical Intervention (MMI)

	Needing MMI (n = 159)	Not Needing MMI (n = 106)	*P**
Age, median (IQR), y	1.8 (1.0–2.8)	2.7 (1.7–4.7)	<0.001†
Male sex	82 (51.6%)	62 (58.5%)	0.27
Hospitalized	159 (100%)	16 (11.2%)	<0.001
Days sick on inclusion, median (IQR)	4 (2–5)	4 (2–6)	0.49†
High temperature ≥38.5°C	125 (78.6%)	89 (84.0%)	0.076
Presence of hypoxemia (Spo_2 ≤92%)	63 (39.6%)	6 (5.7%)	<0.001
Tachypnea present	142 (89.3%)	59 (55.7%)	<0.001
Chest retraction score, median (IQR)	2 (0.75–4)	0 (0–1)	<0.001†
Chest retraction score ≥6	32 (20.1%)	1 (0.9%)	<0.001
PEWS, median (IQR)	4 (2–5)	3 (1–4)	<0.001†
PEWS ≥3	111 (69.8%)	46 (43.4%)	0.022
Laboratory findings			
CRP, median (IQR), mg/L	90 (36–180)	70 (22.5–195)	0.24†
WBC count, median (IQR), $\times 10^9$/L	11.8 (9.3–17.9)	12.4 (8.1–19.1)	0.82†
Radiological findings			
Multifocal changes	93 (58.5%)	33 (31.1%)	<0.001
Interstitial changes	2 (1.3%)	2 (1.9%)	0.68
Pleural fluid	8 (5.1%)	7 (6.6%)	0.60
Treatment			
No antibiotics given	39 (24.5%)	28 (26.4%)	0.66
Treated with full-course antibiotics‡	93 (58.5%)	62 (58.5%)	0.86

All numbers given as n (% of total in each column), unless were otherwise indicated. Missing data in fewer than 10 cases in all variables with the exception of PEWS (missing data in 39 cases).

*All significance levels are 2-sided and all analyses are χ^2 test, except where indicated.

†Mann-Whitney *U* test.

‡A minimum of 5 days was regarded as full course for all antibiotics except azithromycin, for which 3 days was regarded as a full course.

hand, as sensitivity and negative likelihood ratios are poor, these clinical findings cannot be used to rule out the need for major medical interventions. We found 60% of CAP cases to need 1 or more major medical interventions, similar to the proportion of severe CAP cases in a UK multicenter study with a severity definition comprising the major medical interventions examined in our study.[25]

The recent US multicenter study assessing predictors for severity in pediatric pneumonia also found hypoxemia as one of the strongest clinical predictors of severity in pneumonia.[5] Also, previously hypoxemia has been consistently found as a predictor for serious infection in general[7,26] and considered a key feature in severity assessment in CAP.[3,6,27,28] Furthermore, hypoxemia and respiratory distress have been found by others as (i) important predictors in a study on serious respiratory infections,[13] (ii) associated with supplemental oxygen and fluids in a study on CAP,[25] and (iii) important predictors of the need for a major medical intervention in a study on bronchiolitis.[14] More unexpectedly, age-related tachypnea failed to provide unique significant contribution in predicting the need for major medical interventions in our multivariate analyses, as tachypnea has been found to predict serious infection in general[7,26] and severity in CAP.[25] On the other hand

TABLE 3. Multivariate Logistic Regression Predicting Likelihood of the Need for Major Medical Interventions

	Suspected Pneumonia (n = 394)	Proven Pneumonia (n = 265)
	OR (95% CI)	OR (95% CI)
Presence of hypoxemia (Spo_2 ≤92%)	3.66 (1.75–7.67)*	3.83 (1.46–10.05)*
Chest retraction score†	1.21 (1.05–1.39)*	1.31 (1.07–1.60)*
Presence of age-specific tachypnea	1.00 (0.50–2.02)	1.55 (0.66–3.67)
Modified PEWS†	1.27 (1.08–1.49)*	1.11 (0.91–1.36)
History/findings of temperature ≥38.5°C	1.12 (0.56–2.21)	0.68 (0.26–1.76)
Age in years	0.96 (0.88–1.04)	0.94 (0.86–1.02)

*Unique significant contribution to the model, that is, $P < 0.05$.

†OR for every 1-point increase in the chest retraction score and the modified PEWS, respectively.

© 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 4. Sensitivity, Specificity, and Likelihood Ratios of Clinical and Radiological Predictors for the Need for Major Medical Interventions

	Suspected Pneumonia (n = 394)				**Proven Pneumonia (n = 265)**			
	Sensitivity (95% CI)	Specificity (95% CI)	LR+* (95% CI)	LR−† (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+* (95% CI)	LR−† (95% CI)
Hypoxemia	38% (31%–45%)	94% (90%–97%)	6.4 (3.5–11.7)	0.7 (0.6–0.7)	40% (32%–48%)	94% (87–98%)	6.6 (3.0–14.6)	0.6 (0.6–0.7)
Retraction score ≥6	21% (16%–27%)	97% (94%–99%)	8.0 (3.2–19.9)	0.8 (0.8–0.9)	20% (14%–27%)	99% (95%–100%)	20.9 (2.9–150)	0.8 (0.7–0.9)
PEWS ≥3	75% (68%–81%)	46% (37%–54%)	1.4 (1.2–1.6)	0.6 (0.4–0.8)	75% (67%–81%)	40% (29%–52%)	1.3 (1.0–1.5)	0.6 (0.4–0.9)
1, 2, or all 3 predictors	80% (74%–85%)	44% (36%–53%)	1.4 (1.2–1.7)	0.5 (0.3–0.6)	79% (72%–85%)	39% (28%–51%)	1.3 (1.1–1.6)	0.5 (0.4–0.8)
Consolidation	82% (75%–87%)	48% (40%–54%)	1.5 (1.3–1.8)	0.4 (0.3–0.6)	—	—	—	—
Multifocal changes	51% (44%–58%)	76% (69%–82%)	2.1 (1.6–2.8)	0.7 (0.6–0.8)	59% (50%–66%)	69% (59%–78%)	1.9 (1.4–2.6)	0.6 (0.5–0.8)
1, 2, or all 3 predictors + consolidation	64% (57%–71%)	72% (65%–79%)	2.3 (1.8–3)	0.5 (0.4–0.6)	—	—	—	—
1, 2, or all 3 predictors + multifocal	76% (66%–83%)	60% (53%–65%)	1.9 (1.6–2.2)	0.4 (0.3–0.6)	50% (42%–58%)	80% (71%–87%)	2.5 (1.6–3.8)	0.6 (0.5–0.8)

Sensitivity, specificity, and likelihood ratios were calculated with an online statistical calculator (www.medcalc.org).

*LR+: likelihood ratio of positive test; sensitivity/(1 − specificity), that is, denotes ratio between true-positive and false-positive test results.

† LR−: likelihood ratio of negative test; 1 − sensitivity/specificity, that is, denotes ratio between false-negative and true-negative results.

© 2017 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 5. The Need for Major Medical Intervention (MMI) by Etiology Stratified by Age

	Suspected Pneumonia (n = 394)			Proven Pneumonia (n = 265)		
	Needing MMI	Not Needing MMI	*P**	Needing MMI	Not Needing MMI	*P**
All ages	n = 166	n = 166		n = 137	n = 86	
Viral	134 (80.7%)	122 (73.5%)		107 (78.1%)	61 (70.9%)	
Atypical	7 (4.2%)	19 (11.5%)	0.047	7 (5.1%)	14 (16.3%)	0.019
Bacterial	25 (15.1%)	25 (15.1%)		23 (16.8%)	11 (12.8%)	
Age <2 y	n = 107	n = 72		n = 84	n = 30	
Viral	88 (82.2%)	59 (81.9%)		67 (79.8%)	26 (86.7%)	
Atypical	2 (1.9%)	1 (1.4%)	0.96	2 (2.4%)	0	0.57
Bacterial	17 (15.9%)	12 (16.7%)		15 (17.9%)	4 (13.3%)	
Age 2–5 y	n = 50	n = 68		n = 45	n = 37	
Viral	42 (84%)	52 (76.5%)		37 (82.2%)	30 (81.1%)	
Atypical	2 (4%)	4 (5.9%)	0.60	2 (4.4%)	1 (2.7%)	0.87
Bacterial	6 (12%)	12 (17.6%)		6 (13.3%)	6 (16.2%)	
Age >5 y	n = 9	n = 26		n = 8	n = 19	
Viral	4 (44.4%)	11 (42.3%)		3 (37.5%)	5 (26.3%)	
Atypical	3 (33.3%)	14 (53.8%)	0.20	3 (37.5%)	13 (68.4%)	0.21
Bacterial	2 (22.2%)	1 (3.8%)		2 (25%)	1 (5.3%)	

Percentages shown are of total number in each age and severity group; cases with no cause found were excluded.

*χ^2 Test comparing the proportion of severe versus nonsevere cases in the 3 etiology groups; cases with no cause found were excluded.

and more in line with our findings, in the recent US study, tachypnea's statistical significance in predicting severity seemed relatively weak, with ORs close to 1 and nonsignificant individual contribution to several of the prognostic models.[5] Our findings of tachypnea not predicting severity may be related to the new epidemiological situation after pneumococcal vaccination, the low specificity of this clinical variable, and perhaps also our chosen age-related cutoffs, but cannot be fully explained, as this study was not designed to explore this. Young age is associated with severity in CAP,[1,5,27] and although significantly associated with the need for major medical interventions in univariate analyses, young age failed to significantly predict this need in our multivariate model, perhaps because of a high proportion of the youngest children in the cohort. The modified PEWS can be used to predict deterioration,[23,29] but in our study was found to predict the need for major medical interventions in multivariate analyses only in suspected and not proven CAP cases. One reason for this may be that a cutoff of 3 points for PEWS may be too low to detect deterioration in children with radiologically proven pneumonia, because PEWS assesses circulatory variables and the neurological condition of the child in addition to respiratory findings. Although including PEWS of 3 or greater improved sensitivity, the specificity was reduced (Table 4). The inflammatory markers CRP and WBC count did not predict the need for major medical interventions, but radiological findings were associated with the need for major medical interventions. Multifocal radiological change is proposed as a criterion for severity by one of the major guidelines for CAP,[4] and both our findings and those of the recent US pneumonia severity study support this.[5] In age-stratified analyses, no association between viral, atypical, or bacterial etiology and the need for a major medical intervention was found, and antibiotic prescription was just as common regardless of the need for a major medical intervention. This is in contrast to the aforementioned US study, but although bacterial etiology was associated with severity in that study, adding etiology data had negligible impact on their prognostic models.[5]

We see our 2-step approach of analyzing the predictive ability of both clinical features, radiological findings and inflammatory markers, first in cases clinically suspected to have pneumonia then second in those with proven pneumonia, as a major strength of the study. This will mimic the diagnostic process in the emergency room and make our results easily transferable to everyday clinical practice. Given the substantial overlap of clinical features in ALRIs and the problems in defining pneumonia,[30,31] cases of bronchiolitis may have been included as suspected cases of pneumonia (although chest radiography is not routine in bronchiolitis in our department). On the other hand, we believe our definition makes it less likely that we missed cases of radiological pneumonia. Patients not admitted were not reassessed routinely but were encouraged to come back if worsening. Although clinicians on call were urged to collect new clinical variables in patients initially treated ambulatory who were admitted upon recontact, we cannot fully exclude that we missed some ambulatory-treated children in need of a major medical intervention at a later stage. Hypoxemia at inclusion as a predictor variable will naturally overlap the outcome of oxygen requirements during admission, but is not the same. In many cases, low Spo_2 at admission will be resolved by simpler measures such as inhaled medications. Although not all potential clinical severity predictors are included, we believe our constellation of selected predictors (including specific features and more general measures such as the modified PEWS) cover most important aspects of assessing severity in pediatric pneumonia. One aspect that may not be covered and constitutes a weakness in this study is that no measures for intermittent apnea are included. Clinical features were measured in a routine clinical setting by the attending nurse or doctor and could have introduced data collection error, although all staff is trained in these routine measurements. Furthermore, interrater reliability for the clinical variables was not measured, and this limitation must be considered before using our results in clinical practice. For PEWS and the chest retraction score, interrater reliability has been measured by others with acceptable results.[21,32]

© 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

The attending clinician determined treatment, and this constitutes a potential source of bias. Administering supplementary fluids is an intervention often based on subjective considerations. Hence, a subsidiary analysis excluding supplemental fluid from the major medical interventions was done, and this analysis provided better ORs for hypoxemia and respiratory distress in the multivariate model, whereas PEWS lost its significant contribution. For most variables, there were minimal missing data. However, for PEWS, only 82% of data were complete, which may influence its predictive power. With relatively few atypical and bacterial cases, conclusions on the association between etiology and the need for 1 or more major medical interventions must be interpreted cautiously. Furthermore, and as discussed in our previous publication,[17] there are several obstacles in the microbiological diagnosis of pneumonia, introducing some uncertainty in our etiological classification that may influence our results. On the other hand, the validity of our etiological results is corroborated by similar results in a recent, large US multicenter CAP study.[18] Given the observational and 1-center setting of the present study, representativeness must be kept in mind when extrapolating our results to other populations.

In conclusion, we provide evidence that in the post–pneumococcal vaccination era the prediction of more severe pneumonia requiring 1 or more major medical interventions and hence hospitalization primarily depends on the presence or absence of hypoxemia and an assessment of distressed breathing. Our findings support a good rule in ability for more severe pneumonia for these 2 clinical predictors, but given the poor sensitivity and negative likelihood ratio, they cannot be used to rule out more severe pneumonia. Chest radiography findings can give additional information when assessing severity and the need for hospitalization, whereas testing of CRP or WBC count does not. Etiology does not seem to be associated with the need for major medical interventions. Our findings may help to improve management guidelines in pediatric CAP. Further research should aim at defining sensitive predictors and a validated scoring system for severity in pediatric pneumonia.

ACKNOWLEDGMENTS

The authors thank all participating children and their parents. They also thank the doctors and nurses on call at the Department of Pediatric and Adolescent Medicine, Akershus University Hospital, for help in the recruitment of patients and in collecting data. Furthermore, they thank Drs R. Bull and R. Grotli at the Department of Radiology, Akershus University Hospital, for radiological examinations; Drs I. Aaberge and A. Aase for pneumococcal serological analyses at the Department of Bacteriology and Immunology, the Norwegian Institute for Public Health; and the staff at the laboratories at Akershus University Hospital for all other laboratory analyses.

REFERENCES

1. Clark JE, Hammal D, Hampton F, et al. Epidemiology of community-acquired pneumonia in children seen in hospital. *Epidemiol Infect*. 2007;135:262–269.
2. Forster J, Ihorst G, Rieger CH, et al. Prospective population-based study of viral lower respiratory tract infections in children under 3 years of age (the PRI.DE study). *Eur J Pediatr*. 2004;163:709–716.
3. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;66(suppl 2):ii1–ii23.
4. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53:e25–e76.
5. Williams DJ, Zhu Y, Grijalva CG, et al. Predicting severe pneumonia outcomes in children. *Pediatrics*. 2016;138:e20161019.
6. Principi N, Esposito S. Management of severe community-acquired pneumonia of children in developing and developed countries. *Thorax*. 2011;66:815–822.
7. Van den Bruel A, Haj-Hassan T, Thompson M, et al. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. *Lancet*. 2010;375:834–845.
8. Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. *BMJ*. 2011;342:d3082.
9. Lynch T, Platt R, Gouin S, et al. Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? *Pediatrics*. 2004;113(3 pt 1):e186–e189.
10. Rothrock SG, Green SM, Fanelli JM, et al. Do published guidelines predict pneumonia in children presenting to an urban ED? *Pediatr Emerg Care*. 2001;17:240–243.
11. Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, et al. Identifying children with pneumonia in the emergency department. *Clin Pediatr (Phila)*. 2005;44:427–435.
12. Palafox M, Guiscafré H, Reyes H, et al. Diagnostic value of tachypnoea in pneumonia defined radiologically. *Arch Dis Child*. 2000;82:41–45.
13. Blacklock C, Mayon-White R, Coad N, et al. Which symptoms and clinical features correctly identify serious respiratory infection in children attending a paediatric assessment unit? *Arch Dis Child*. 2011;96:708–714.
14. Parker MJ, Allen U, Stephens D, et al. Predictors of major intervention in infants with bronchiolitis. *Pediatr Pulmonol*. 2009;44:358–363.
15. Grafakou O, Moustaki M, Tsolia M, et al. Can chest x-ray predict pneumonia severity? *Pediatr Pulmonol*. 2004;38:465–469.
16. Kin Key N, Araujo-Neto CA, Nascimento-Carvalho CM. Severity of childhood community-acquired pneumonia and chest radiographic findings. *Pediatr Pulmonol*. 2009;44:249–252.
17. Berg AS, Inchley CS, Aase A, et al. Etiology of pneumonia in a pediatric population with high pneumococcal vaccine coverage: a prospective study. *Pediatr Infect Dis J*. 2016;35:e69–e75.
18. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372: 835–845.
19. Angoulvant F, Levy C, Grimprel E, et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. *Clin Infect Dis*. 2014;58:918–924.
20. Gove S. Integrated management of childhood illness by outpatient health workers: technical basis and overview. The WHO Working Group on Guidelines for Integrated Management of the Sick Child. *Bull World Health Organ*. 1997;75(suppl 1):7–24.
21. Lowell DI, Lister G, Von Koss H, et al. Wheezing in infants: the response to epinephrine. *Pediatrics*. 1987;79:939–945.
22. Hinchliffe R. Reference values. In: Lilleyman J, Hann I, eds. *Pediatric Hematology*. 2nd ed. Edinburgh: Churchill Livingstone; 1992:1–22.
23. Solevåg AL, Eggen EH, Schröder J, et al. Use of a modified Pediatric Early Warning Score in a department of pediatric and adolescent medicine. *PLoS One*. 2013;8:e72534.
24. Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ*. 2005;83:353–9.
25. Clark JE, Hammal D, Spencer D, et al. Children with pneumonia: how do they present and how are they managed? *Arch Dis Child*. 2007;92: 394–398.

 © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

26. Thompson M, Coad N, Harnden A, et al. How well do vital signs identify children with serious infections in paediatric emergency care? *Arch Dis Child*. 2009;94:888–893.

27. Esposito S, Cohen R, Domingo JD, et al. Antibiotic therapy for pediatric community-acquired pneumonia: do we know when, what and for how long to treat? *Pediatr Infect Dis J*. 2012;31:e78–e85.

28. Reed C, Madhi SA, Klugman KP, et al. Development of the Respiratory Index of Severity in Children (RISC) score among young children with respiratory infections in South Africa. *PLoS One*. 2012; 7:e27793.

29. Akre M, Finkelstein M, Erickson M, et al. Sensitivity of the Pediatric Early Warning Score to identify patient deterioration. *Pediatrics*. 2010;125: e763–e769.

30. McIntosh K. Community-acquired pneumonia in children. *N Engl J Med*. 2002;346:429–437.

31. Langley JM, Bradley JS. Defining pneumonia in critically ill infants and children. *Pediatr Crit Care Med*. 2005;6(suppl 3):S9–S13.

32. Tucker KM, Brewer TL, Baker RB, et al. Prospective evaluation of a pediatric inpatient early warning scoring system. *J Spec Pediatr Nurs*. 2009;14:79–85.

© 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

AQ1 = Please check if authors name are correctly captured for given names (in red) and surnames (in blue) for indexing after publication.

AQ2 = Please indicate location of GE Healthcare.

AQ3 = Please indicate name of city in the location of manufacturers "Bosch and Son" and "Covidien."

AQ4 = Please indicate name and location of the manufacturer of IBM SPSS Statistics version 22.

END OF AUTHOR QUERIES

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.