# Clinical features and inflammatory markers in pediatric pneumonia: a prospective study

Are Stuwitz Berg, [1,*,2]

Phone +47 92 444 689
Email arebe@medisin.uio.no
AQ1

Christopher Stephen Inchley, [1]

Email: christopher.inchley@medisin.uio.no

Hans Olav Fjaerli, [1]

Email hans.olav.fjaerli@ahus.no

Truls Michael Leegaard, [3,2]

Email truls.michael.leegaard@ahus.no

Morten Lindbaek, [4]

Email morten.lindbak@medisin.uio.no

Britt Nakstad, [1,2]

Email britt.nakstad@medisin.uio.no

[1] Department of Pediatric and Adolescent Medicine, Akershus University Hospital, Postal Box 1000, 1478 Lørenskog, Norway

[2] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[3] Department of Microbiology and Infection Control, Akershus University Hospital, Lørenskog, Norway

[4] Institute of Health and Society, Faculty of Medicine, University of

Oslo, Oslo, Norway

# Abstract

In this prospective, observational study on previously healthy children <18 years, we aimed to study the diagnostic ability of clinical features and inflammatory markers to (i) predict pathologic chest radiography in suspected pneumonia and (ii) differentiate etiology in radiological proven pneumonia. In 394 cases of suspected pneumonia, 265 (67%) had radiographs consistent with pneumonia; 34/265 had proof of bacterial etiology. Of the cases, 86.5% had received pneumococcal conjugate vaccine. In suspected pneumonia, positive chest radiography was significantly associated with increasing C-reactive protein (CRP) values, higher age, and $SpO_2$ ≤92% in multivariate logistic regression, OR 1.06 (95% CI 1.03 to 1.09), OR 1.09 (95% CI 1.00 to1.18), and OR 2.71 (95% CI 1.42 to 5.18), respectively. In proven pneumonia, bacterial pneumonia was significantly differentiated from viral/atypical pneumonia by increasing CRP values and $SpO_2$ >92% in multivariate logistic regression, OR 1.09 (95% CI 1.05 to 1.14) and OR 0.23 (95% CI 0.06 to 0.82), respectively. Combining high CRP values (>80 mg/L) and elevated white blood cell (WBC) count provided specificity >85%, positive likelihood ratios >3, but sensitivity <46% for both radiographic proven and bacterial pneumonia.

*Conclusion*: With relatively high specificity and likelihood ratio CRP, WBC count and hypoxemia may be beneficial in ruling in a positive chest radiograph in suspected pneumonia and bacterial etiology in proven pneumonia, but with low sensitivity, the clinical utility is limited.

| **What is Known:** |
| --- |
| • *Pneumonia is recommended to be a clinical diagnosis, and neither clinical features nor inflammatory markers can reliably distinguish etiology.* |
| • *The etiology of pneumonia has changed after routine pneumococcal conjugate vaccine.* |
| **What is New:** |
| • *High CRP and WBC counts were associated with infiltrates in children with suspected pneumonia and with bacterial infection in proven pneumonia.* |

• *In the post-pneumococcal vaccination era, viral etiology is expected, and in cases of pneumonia with low CRP and WBC counts, a watch-and-wait strategy for antibiotic treatment may be applied.*

## Keywords

Pneumonia
Clinical features
Inflammatory markers
Pneumococcal vaccination

### Abbreviations

| | |
|---|---|
| ALRI | Acute lower respiratory tract infection |
| AUC | Area under the curve |
| CAP | Community-acquired pneumonia |
| CRP | C-reactive protein |
| IQR | Interquartile range |
| PCR | Polymerase chain reaction |
| ROCs | Receiver operating characteristics |
| WBC | White blood cells |

Communicated by David Nadal

# Introduction

WHO and major International Management Guidelines recommend that the diagnosis of community-acquired pneumonia (CAP) in children should be based on clinical criteria [4, 13, 15] and that routine measurements of inflammatory markers or routine chest radiography are not warranted, as these investigations cannot reliably distinguish between viral and bacterial etiologies [4, 15]. Based on clinical signs and symptoms, it is difficult to distinguish pneumonia from other pediatric acute lower respiratory tract infections (ALRIs) [27], and a recent systematic review and meta-analysis highlights these difficulties [33]. The etiology of pediatric CAP has changed in areas where the pneumococcal conjugate vaccine has been introduced in routine immunization programs. In a

previous publication of this cohort, we observed an increase in the proportion of viral etiology and a consequent decrease in bacterial etiology in 265 cases of radiologically proven CAP cases [2], a finding consistent with other recent CAP etiology studies [1, 19]. This change in etiology may have an impact on various clinical signs and symptoms of CAP and may alter the diagnostic ability of clinical features and inflammatory markers. The diagnostic ability of inflammatory markers in pediatric CAP in the post-pneumococcal vaccination era has recently been reported [9], but as pointed out, clinical features are viewed as crucial in diagnosing pediatric CAP. We therefore wanted to examine the diagnostic ability of clinical features combined with inflammatory markers in a population with a high pneumococcal vaccination rate.

The present study was performed in a routine clinical setting, examining previously healthy children and adolescents. Childhood immunization rates are >90% in the Norwegian pediatric population [38]. The 7-valent pneumococcal conjugate vaccine was introduced in the Norwegian Childhood Immunization program in 2006 and replaced with the 13-valent vaccine in 2011. We aimed to find if clinical features, C-reactive protein (CRP), or white blood cell (WBC) count can (1) predict a chest radiography consistent with pneumonia in clinically suspected CAP or (2) differentiate bacterial from viral and/or atypical pneumonia in radiologically proven CAP.

# Materials and methods

## Study design and population

This prospective, observational diagnostic study was conducted at the Department of Pediatric and Adolescent Medicine, Akershus University Hospital, Norway, from 1 January 2012 to 1 January 2014. Children and adolescents 0–18 years of age were considered for inclusion and recruited by either (i) the attending physician in the pediatric emergency room (ambulatory and hospitalized patients) or (ii) the primary care physician where referral to hospital was not seen as necessary. Eligible patients were included in two steps. First, the inclusion criteria into the cohort of clinically suspected CAP cases were (1) measured body temperature >37.5 °C at inclusion or a history of fever to assure the acuteness of the current infection, (2) clinical sign(s) of lower respiratory tract infection (tachypnea, chest retractions, cough), and (3) either a

chest radiograph ordered by the attending clinician due to suspected pneumonia in patients enrolled in hospital (admitted or ambulatory treated) or intention to treat with antibiotics due to clinical suspicion of pneumonia in patients enrolled in primary care. Patients enrolled from primary care were sent to the hospital for chest radiography and diagnostic tests the following day. Secondly, the inclusion criteria into the cohort of proven pneumonia consisted of all in the clinically suspected cohort who were found to have a chest radiograph consistent with pneumonia as described below. Exclusion criteria were severe motor impairment, innate or iatrogenic immunodeficiency, cystic fibrosis or other chronic disease that predisposes for pneumonia, or becoming sick while in hospital or abroad.

Patients over 16 years of age or parents/guardians of younger patients signed a written informed consent. The Regional Ethics Committee and the local Data Protection Officer approved the study.

## Definition of outcomes

A chest radiograph was taken at inclusion, blinded for clinical data, and examined independently by two study radiologists experienced in pediatric radiology [2]. Localized or interstitial infiltrates were regarded as findings consistent with pneumonia except for radiographs with only perihilar changes [5]. To increase specificity, only findings identified by both radiologists were labeled positive, as interrater variability can be substantial in pediatric chest radiography, especially in non-alveolar findings [5].

To identify etiology, a number of microbiological diagnostic tests were performed and these tests and their results have previously been published [2]. 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 seven 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 (RSV) A/B, influenza virus A/B, parainfluenza virus 1–3, adenovirus (all complement fixation tests), *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Streptococcus pneumoniae* (ELISA for IgG against pneumolysin and the novel flow cytometric analysis of binding of serum antibodies to live pneumococci

which was strongly correlated to the more widely used pneumolysin ELISA test) [2]; and (3) molecular diagnostic tests (PCR) of nasopharyngeal specimens (obtained in 97% of suspected CAP cases) tested for RSV 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 PCR findings were done with a strict cycle threshold cutoff of 35 to diminish false positives). Based on a positive bacterial culture, a positive serological test and/or positive PCR according to previously described diagnostic criteria [2], all CAP cases were categorized as (1) viral pneumonia without evidence of bacterial co-infection; (2) atypical pneumonia, infections with *M. pneumoniae* and/or *C. pneumoniae*, alone or co-infected with virus; or (3) bacterial pneumonia, infections with all other bacteria, predominantly *S. pneumoniae*, alone or co-infected with virus.

## Clinical variables

The attending physician completed a questionnaire on the patient's medical history and clinical findings at recruitment. Missing information was extracted from the hospital's electronic patient record. A certain and substantial fever was defined as body temperature ≥38.5 °C as measured at the hospital (Bosotherm Basic rectal thermometer, Bosch and Son, Germany or Genius2 tympanic thermometer, Covidien, MA, USA) or as reported by patients (to reduce the impact of previous antipyretic treatment). Respiratory rate was counted for one full minute and defined as tachypnea if <1 month >70 breaths/min, <1 year >50 breaths/min, <3 years >40 breaths/min, and >3 years >30 breaths/min [36]. Hypoxemia was defined as peripheral oxygen saturation ($SpO_2$) ≤92% measured by pulse oximetry (Dash 5000 patient monitor, GE Healthcare). Pediatric nurses in the pediatric emergency room measured body temperature, respiratory rate, and $SpO_2$. Chest retraction score from the Respiratory Distress Assessment Instrument with assessment of supraclavicular, intercostal, and subcostal retractions (one point for mild, two for moderate, and three for marked retractions; maximum nine points) was used as a measure of labored breathing and assessed by the attending physician [24]. In addition, he/she recorded cough and auscultatory findings, which are expiratory wheeze, localized fine crackles, and reduced breath sounds either side.

## Laboratory variables

CRP (mg/L) and WBC count ($10^9$/L), including differential count, were routinely analyzed on enrolment. WBC count is presented as an absolute count and age-adjusted ratio (absolute WBC count divided by the patient's age-specific upper reference range level <1 month 21.0, 2–5 months 19.5, 6 months to 1 year 17.5, 2–5 years 17.0, 6–12 years 14.0, and >13 years 13.0 × $10^9$/L) [18], and neutrophils are presented as the percentage of the total WBC count.

## Analyses

All statistical analyses were done using IBM SPSS Statistics version 22. Significance levels were two sided and set at $p < 0.05$. Categorical data was analyzed with chi-squared test. Continuous data were not normally distributed, hence presented as median with interquartile range (IQR) as a measure of variation and analyzed with Mann-Whitney *U* test or Kruskal-Wallis test. Cases with missing variables were not included in the statistical analyses.

Receiver operating characteristic (ROC) curves were used to examine the discriminatory performance of a continuous variable (CRP) in dichotomous outcomes ("radiography positive versus radiography negative cases in suspected CAP" and "bacterial versus viral/atypical CAP" with those missing etiology excluded).

Logistic regression was performed to assess the ability of several factors to predict the outcome "positive compared to negative chest radiography in suspected pneumonia" and to predict the outcome "bacterial compared to viral and atypical CAP cases" (performed separately and together, those with missing etiology excluded). A simultaneous entry approach was used with a selection of predictor variables on clinical grounds and in line with previous literature [22, 25, 30]~~,~~: presence of tachypnea, localized fine crackles, localized reduced breath sounds, fever ≥38.5 °C, presence of hypoxemia (all categorical), CRP values, and age. CRP was chosen above WBC count in line with previous literature [39] and to avoid co-linearity. Interaction was checked between age and all other variables, and significant interactions are reported.

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

# Results

## The patient cohort

Of the patients with suspected CAP, 394 were enrolled, of which 265 cases had radiological findings consistent with pneumonia (Fig. 1). Two hundred sixty one of the 265 had focal radiological findings, and 4/265 had interstitial radiological changes. Fifteen of the 265 had parapneumonic effusions, of which 7 were regarded as complicated parapneumonic effusion/empyema and tapped [3]. One-hundred-twenty-nine patients did not have radiological findings consistent with pneumonia (82 with normal chest radiograph and 42 with only perihilar involvement, 5 with other findings, and all 129 cases are denoted as radiography negative in the following). Details on demographic, clinical, and laboratory characteristics by age in all 265 CAP cases compared to the 129 radiography negative cases are presented in Table 1. Univariate analyses show that children with radiological proven CAP were older; had higher rates of hospitalization, hypoxemia, and localized reduced breath sounds; and had higher CRP values and percentage of neutrophils compared to the radiography negative cases. Seven of the 265 cases were <3 months old. ~~The~~ 84.9% of the CAP cases and 89.8% of the radiography negative cases had received one or more doses of pneumococcal conjugate vaccine. Of the 394 suspected CAP cases, 220 were hospitalized, 104 treated ambulatory at hospital level, and 68 treated in primary care (Fig. 1). Clinical data were missing in less than 5/394 cases for most variables, for cough in 14/394, and for measured temperature in 12/394 cases.

**Fig. 1**

Patient inclusion

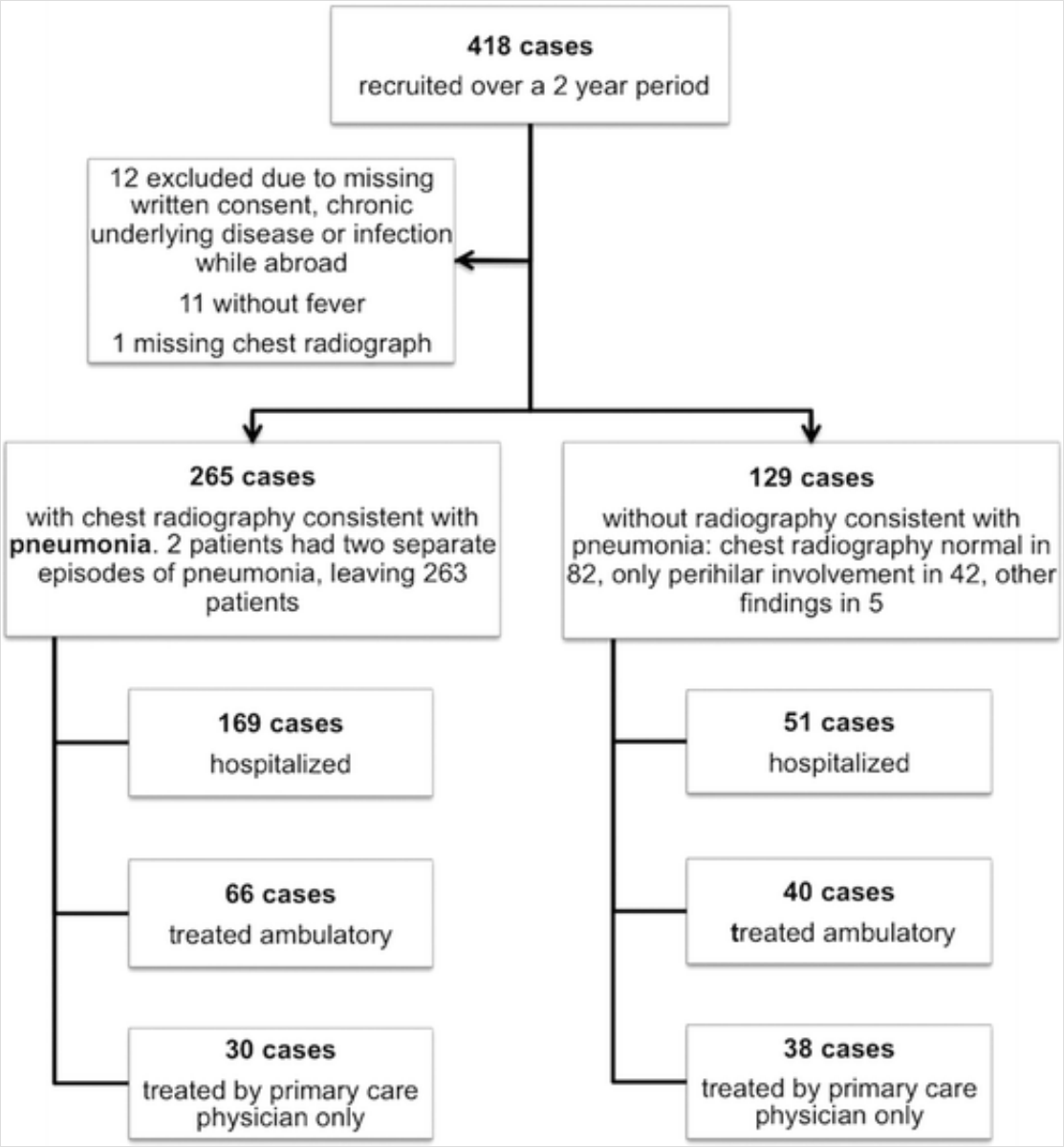



**Table 1**

Demographic, clinical, and laboratory characteristics at inclusion of 265 cases of ra CAP by age, compared to 129 radiograph negative cases

| | <2 years (*n* = 127) | 2–5 years (*n* = 98) | >5 years (*n* = 40) | Significance[a] | All CAP cases (*n* = 265) | Radiog nega cas (*n* = |
|---|---|---|---|---|---|---|
| Age in years, median (IQR) | 1.2 (0.6–1.6) | 2.8 (2.3–3.7) | 9 (6.4–14.9) | | 2 (1.3–3.6) | 1.7 (1. |
| Male gender | 73 (57.5%) | 46 (46.9%) | 25 (62.5%) | $p = 0.15$ | 144 (54.3%) | 76 (60 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hospitalized | 93 (73.2%) | 58 (59.2%) | 18 (45%) | $p = 0.003$* | 169 (63.8%) | 51 (39. |
| Days sick on inclusion, median (IQR) | 4 (2–5) | 4 (2–6) | 3 (2–6) | $p = 0.55$[b] | 4 (2–6) | 4 (2–5. |
| Fever ≥38.5 °C | 104 (81.9%) | 79 (80.6%) | 31 (77.5%) | $p = 0.91$ | 214 (80.8%) | 96 (74. |
| Cough | 111 (87.4%) | 90 (91.8%) | 36 (90%) | $p = 0.72$ | 237 (89.4%) | 116 (8 |
| Tachypnea, age specific | 102 (80.3%) | 75 (76.5%) | 24 (60%) | $p = 0.014$* | 201 (75.8%) | 89 (70 |
| Hypoxemia ($SpO_2$ ≤92%) | 34 (26.8%) | 31 (31.6%) | 4 (10%) | $p = 0.026$* | 69 (26%) | 15 (11. |
| Chest retraction score, median (IQR) | 2 (0–4) | 2 (0–4) | 0 (0–0) | $p < 0.001$[b, *] | 1 (0–3) | 1 (0–2 |
| Auscultatory findings | | | | | | |
| Wheeze | 25 (19.7%) | 21 (21.4%) | 2 (5%) | $p = 0.059$ | 48 (18.1%) | 28 (21. |
| Fine crackles | 31 (24.4%) | 20 (20.4%) | 10 (25%) | $p = 0.75$ | 61 (23%) | 27 (20. |
| Reduced breath sounds | 11 (8.7%) | 19 (19.4%) | 15 (37.5%) | $p < 0.001$* | 45 (17%) | 11 (8.5 |
| Laboratory findings | | | | | | |
| CRP (mg/L), median (IQR) | 75 (30–160) | 90 (26–190) | 90 (45–240) | $p = 0.86$ [b] | 80(32–190) | 42 (13- |
| WBC count ($\times 10^9$/L), median (IQR) | 11.6 (9.4–17.6) | 11.4 (7.8–17.6) | 9.2 (6.2–15.3) | $p < 0.001$[b, *] | 12.2 (8.9–18.1) | 11.3 (8 15.8) |
| Age-adjusted WBC count | 29 (22.8%) | 30 (32.7%) | 16 (40%) | $p = 0.11$[b] | 75 (28.7%) | 22 (17. |

| | | | | | | |
|---|---|---|---|---|---|---|
| elevation[e] | | | | | | |
| Percentage neutrophils, median (IQR) | 49 (38–66) | 67(52–77) | 71 (65–87) | $p < 0.001$[b, *] | 64 (46–76) | 52 (37- |

All numbers given as *n* (percent of total in each column), except where otherwise in

*Significant differences

[a]Comparison between the three age groups. All significance levels are two sided and squared test except where otherwise indicated

[b]~~All significance levels are two sided and all analyses are chi-squared test, except~~ K

[c]Comparison between all CAP cases and other ALRI cases. All significance levels a analyses are chi-squared test except where otherwise indicated

[d]~~All significance levels are two sided and all analyses are chi-squared test, except~~ M

[e]Proportion of cases with age-adjusted WBC count ratio >1

## Etiological distribution

Of the 265 radiological proven cases of CAP, 63.4% were viral, 7.9% atypical bacterial, 12.8% bacterial causes (11.3% pneumococcus, 9.4% with viral co-infection), and 15.8% without any proven microbiological agent [2]. The distribution of viral, atypical, and bacterial CAP according to place of treatment was significantly different ($p = 0.03$, chi-squared test), with a lower proportion of bacterial cases in primary care and a lower proportion of atypical cases in the hospitalized group (viral, atypical, and bacterial CAP in primary care patients 63.3, 16.7, and 3.3%, respectively; in ambulatory treated patients 57.6, 12.1, and 12.1%; and hospitalized patients 65.7, 4.7, and 14.8%). Clinical and laboratory characteristics by etiology are presented in Table 2, and univariate analyses show that (1) atypical pneumonia was associated with older patients, fewer hospitalizations, and longer duration of disease and with a tendency of less often being tacyhpnoeic; (2) viral pneumonia was associated with being hypoxemic and a greater degree of dyspnea; and (3) bacterial pneumonia was associated with higher CRP values and WBC count. CAP cases without wheeze (217/265) showed a similar distribution of etiological agents~~,~~: viral pneumonia 60.9%, atypical pneumonia 8.8%, and bacterial pneumonia 14%, as did those

with tachypnea (201/265)~~,~~: viral pneumonia 65.4%, atypical pneumonia 6%, and bacterial pneumonia 13.9%.

**Table 2**

Clinical features and inflammatory markers at inclusion by etiology of 265 cases of radiological confirmed CAP

| | **Viral pneumonia (*n* = 168)** | **Atypical pneumonia (*n* = 21)** | **Bacterial pneumonia (*n* = 34)** | **Significance[a]** | **No cause found (*n* = 42)** |
|---|---|---|---|---|---|
| Age in years, median (IQR) | 1.8 (1.1–2.7) | 9.6 (5–14.3) | 1.7 (1.1–2.9) | $p < 0.001$[b, *] | 3.3 (1.8–7.3) |
| Male gender | 92 (54.8%) | 11 (52.4%) | 19 (55.9%) | $p = 0.97$ | 22 (53.4%) |
| Hospitalized | 111 (66.1%) | 8 (38.1%) | 25 (73.5%) | $p = 0.020$ | 24 (57.1%) |
| Days sick on inclusion, median (IQR) | 4 (2–6) | 5 (3–9.5) | 3 (2–4) | $p = 0.014$[b, *] | 2 (2–4) |
| Fever ≥38.5 °C | 135 (80.4%) | 16 (76.2%) | 31 (91.2%) | $p = 0.39$ | 32 (76.2%) |
| Cough | 154 (92.3%) | 19 (90.5%) | 29 (85.3%) | $p = 0.45$ | 35 (83.3%) |
| Tachypnea, age specific | 132 (78.6%) | 12 (57.1%) | 28 (82.4%) | $p = 0.053$ | 29 (69.1%) |
| Hypoxemia ($SpO_2$ ≤92%) | 54 (32.1%) | 4 (19.1%) | 3 (8.8%) | $p = 0.013$* | 8 (19.1%) |
| Chest retraction score, median (IQR) | 2 (0–4) | 0 (0–1) | 0.5 (0–3) | $p = 0.002$[b, *] | 0 (0–2) |
| Auscultatory findings | | | | | |
| Wheeze | 36 (21.4%) | 2 (9.5%) | 4 (11.8%) | $p = 0.21$ | 6 (14.3%) |

| | | | | | |
|---|---|---|---|---|---|
| Fine crackles, localized | 41 (24.4%) | 6 (28.6%) | 6 (17.6%) | $p = 0.60$ | 8 (19.0%) |
| Reduced breath sounds, localized | 22 (13.1%) | 6 (28.6%) | 8 (23.5%) | $p = 0.093$ | 9 (21.4%) |
| Laboratory findings | | | | | |
| CRP (mg/L), median (IQR) | 70 (27–150) | 48 (29–105) | 260 (54–320) | $p < 0.001$[b, *] | 160 (75–265) |
| WBC count ($\times 10^9$/L), median (IQR) | 11.1 (8.5–16.1) | 7.3 (6.2–12.1) | 17.1 (10.5–23.2) | $p < 0.001$[b, *] | 16.6 (12.6–23.4) |
| Age-adjusted WBC count elevation | 34 (20.2%) | 3 (14.3%) | 15 (47.1%) | $p = 0.005$[b, *] | 24 (57.1%) |
| Percentage neutrophils, median (IQR) | 56 (43–72) | 69 (59–71) | 70 (50–81) | $p = 0.004$[b, *] | 75 (58–84) |
| All numbers given as *n* (percent of total in each column), except where otherwise indicated | | | | | |
| *Significant differences | | | | | |
| [a]All significance levels are two sided and all statistical analyses are chi-squared test except where otherwise indicated | | | | | |
| [b]~~All significance levels are two sided and all statistical analyses are chi-squared test, except~~ Kruskal-Wallis test | | | | | |

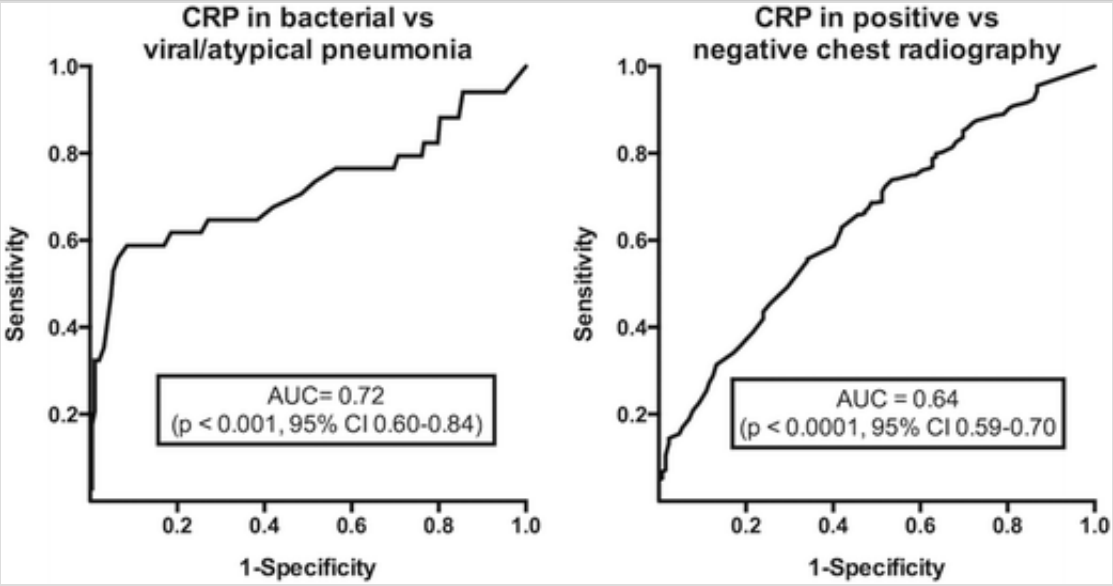
## Inflammatory markers

As stated above, higher median CRP values were significantly associated with both a bacterial cause and a chest radiograph consistent with pneumonia (Tables 1 and 2). A ROC curve provided an area under the curve (AUC) of 0.72 for CRP in separating bacterial from viral or atypical CAP, while a ROC curve for CRP's discriminatory ability for positive versus negative chest radiograph gave

an AUC of 0.64 (Fig. 2). A CRP cutoff value of 80 mg/L corresponded well with the best sensitivity and specificity trade-off in both curves. In univariate analysis, only percentage of neutrophils was significantly associated with positive chest radiography (Table 1), while all three WBC count variables were significantly associated with etiology (Table 2).

**Fig. 2**

Receiver operating characteristics curves for CRP's diagnostic ability in the two main outcomes. *AUC* area under the curve




## Logistic regression analyses and test characteristics

The full logistic regression models for predicting chest radiography consistent with pneumonia and in predicting bacterial CAP compared to viral, atypical, and to viral/atypical CAP were all significant ($p < 0.001$). Three variables provided unique statistically significant contributions to the models, which are increasing CRP (in four/four models), presence/absence of hypoxemia (in three/four models), and older age (in two/four models). Table 3 shows the predictive abilities of the seven independent variables in the four logistic regression models. To mimic the diagnostic process, logistic regression analyses for all four models were also performed in a two-step manner by first introducing the clinical variables and then CRP. This procedure gave similar results as when entering clinical variables and CRP simultaneously.

**Table 3**

Logistic regression predicting likelihood of radiography consistent with pneumonia in suspected CAP and bacterial infection in radiological proven CAP

| | **Positive chest radiography (*n* = 265) versus negative (*n* = 129)** | **Bacterial (*n* = 34) versus viral (*n* = 168) CAP** | **Bacterial (*n* = 34) versus atypical (*n* = 21) CAP** | **Bacterial (*n* = 34) versus viral/atypical CAP (*n* = 189)** |
|---|---|---|---|---|
| | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** |
| Fever ≥38.5 °C | 1.15 (0.64–2.08) | 0.81 (0.21–3.20) | 0.91 (0.06–14.57) | 0.84 (0.22–3.29) |
| Reduced breath sounds | 1.47 (0.68–3.21) | 1.41 (0.42–4.70) | 5.10 (0.25–104.33) | 1.53 (0.48–4.93) |
| Fine crackles | 0.98 (0.56–1.71) | 0.73 (0.25–2.16) | 0.22 (0.02–2.33) | 0.69 (0.24–2.00) |
| Tachypnea | 1.61 (0.93–2.80) | 1.64 (0.57–4.73) | 2.51 (0.24–26.30) | 1.62 (0.56–4.65) |
| Hypoxemia | 2.71 (1.42–5.18)* | 0.22 (0.06–0.80)* | 0.13 (0.01–2.67) | 0.23 (0.06–0.82)* |
| CRP/10[a] | 1.06 (1.03–1.09)* | 1.09 (1.05–1.13)* | 1.10 (1.01–1.20)* | 1.09 (1.05–1.14)* |
| Age in years | 1.09 (1.00–1.18)* | 0.96 (0.78–1.18) | 0.62 (0.44–0.88)* | 0.91 (0.76–1.08) |
| *Variables providing unique statistically significant contributions to the models, CRP (in four/four models), presence/absence of hypoxemia (in three/four models), and age (in two/four models) | | | | |
| [a]OR for the continuous variable CRP/10 denotes the increase in odds ratio for every increase of 10 in CRP | | | | |

Table 4 provides sensitivity, specificity, and likelihood ratios for CRP, age-adjusted WBC count, and the presence of $SpO_2$ ≤92%, alone and in combination. Specificity ranged from 85 to 98% and positive likelihood ratio from 2.4 to 3.3 when combining two or all of the variables in both outcomes, while sensitivity ranged from 4 to 46% when combining two or all variables. Low peripheral oxygen concentration is included as it is the one clinical

variable with unique significant predictive ability in three of the four multivariate models.

**Table 4**

Test characteristics in the main outcomes

| | Sensitivity (95% CI) | Specificity (95% CI) | LR+[a] (95% CI) | LR−[b] (95% CI) |
|---|---|---|---|---|
| Chest radiography consistent with pneumonia in suspected CAP | | | | |
| CRP >80[c] | 55 (49–61) | 66 (57–74) | 1.6 (1.3–2.1) | 0.7 (0.6–0.8) |
| Elevated WBC count[d] | 29 (23–35) | 83 (75–89) | 1.7 (1.1–2.6) | 0.9 (0.8–1) |
| CRP >80 and elevated WBC count | 25 (20–30) | 92 (86–96) | 3.1 (1.7–5.9) | 0.8 (0.7–0.9) |
| Hypoxemia present[e] | 27 (22–33) | 88 (81–93) | 2.2 (1.3–3.8) | 0.8 (0.7–0.9) |
| Hypoxemia present, CRP >80, and elevated WBC count | 4 (2–7) | 98 (94–100) | 2.4 (0.5–11) | 1 (0.9–1) |
| Bacterial versus viral/atypical in proven CAP | | | | |
| CRP >80[c] | 71 (53–85) | 52 (44–59) | 1.5 (1.1–1.9) | 0.6 (0.3–1) |
| Elevated WBC count[d] | 46 (28–64) | 80 (74–87) | 2.3 (1.4–3.7) | 0.7 (0.5–1) |
| CRP >80 and elevated WBC count | 46 (28–64) | 85 (79–90) | 3 (1.8–5) | 0.6 (0.5–0.9) |
| Hypoxemia absent[e] | 91 (76–98) | 31 (25–39) | 1.3 (1.2–1.5) | 0.3 (0.1–0.9) |
| Hypoxemia absent, CRP >80, and elevated WBC count | 39 (23–58) | 88 (82–92) | 3.3 (1.8–5.8) | 0.7 (0.5–0.9) |

| |
|---|
| [a]LR+ likelihood ratio of positive test; sensitivity/(1 − specificity), i.e., denotes ratio between true positive and false positive test results |
| [b]LR− likelihood ratio of negative test; 1 − sensitivity/specificity, i.e., denotes ratio between false negative and true negative |
| [c]Cutoff CRP value of *80* selected from the ROC curves considering best sensitivity/specificity trade-off |
| [d]Age-adjusted WBC counts; *elevated* denotes above upper age-specific reference level |
| [e]The presence of hypoxemia is a positive predictor for the outcome positive chest radiography in suspected CAP but a negative predictor in bacterial proven CAP versus viral/atypical CAP as seen in Table 3 |

# Discussion

In this study, we sought to find clinical features and inflammatory markers that could aid the clinician in predicting the presence of infiltrates in suspected CAP and in predicting bacterial etiology in radiological proven CAP. The non-specific inflammatory markers CRP and WBC count were in a combination of univariate and multivariate analyses found to consistently and significantly predict a positive chest radiograph in clinically suspected pneumonia and bacterial etiology in radiologically proven pneumonia (Tables 1, 2, and 3). The low sensitivity for both CRP and WBC count hampers the clinical utility of these two laboratory tests often used in clinical practice. Furthermore, for CRP, a relatively low but yet significant OR for every increment of 10 mg/L indicates that a substantial increase is needed before a clinical relevant difference in the likelihood of any of the two outcomes is achieved. Hypoxemia at inclusion ($SpO_2$ ≤92%) was the only clinical feature significantly predicting the two main outcomes in both univariate and multivariate analyses, but hypoxemia was only found in less than one third in all subgroups.

Our findings indicate that bacterial pneumonia is associated with a greater degree of inflammation. This is in line with studies performed both before and after implementation of routine pneumococcal immunization [9, 10, 12, 21, 29, 32, 37, 40]. In the ROC curve for CRP's ability to diagnose bacterial pneumonia, a CRP value of 80 mg/L gave the best sensitivity and specificity trade-off. This corresponds to a systematic review on the diagnostic value of laboratory tests in febrile children [39] but is higher than the cutoff

used in a meta-analysis of CRP in pediatric CAP [11]. In one systematic review, WBC count added little extra diagnostic value [39], but by combining CRP and age-related elevated WBC count, we improved the test characteristics. High values of CRP (>80 mg/L) and/or elevated WBC count can significantly rule in bacterial pneumonia (specificity >85% and positive likelihood ratio >3; Table 4), as also found by others [9, 12, 37]. Poor sensitivity reduces their clinical value, as also concluded in a previous systematic review [28]. In predicting positive chest radiography in cases of suspected CAP, a similar statistical association with relatively high specificity and positive likelihood ratios, but with limited clinical utility due to low sensitivity, were found for both CRP and WBC count, in line with a previous study [23]. Although CRP was associated with etiology, the cases treated only in primary care were too few to conclude if our findings collide with a previous primary care study that found no association between CRP and etiology [17]. Furthermore, we found fewer bacterial cases in the primary care group, in line with a study that found predominantly viral cause in ALRI, where the primary care physician considered antibiotics [14].

Previous studies on diagnostic ability of clinical features have focused on their ability to either predict radiographic pneumonia [25, 26, 30, 34, 41] or differentiate etiology [10, 22, 40]. Other studies found reduced peripheral oxygen concentration as one of several clinical features associated with a positive chest radiograph [7, 25, 26, 30, 31], while in our cohort with a high coverage of pneumococcal vaccination and with a large impact of viral etiology, this was the only clinical feature associated with a positive chest radiograph. In differentiating between etiologies in proven CAP, our findings are in line with previous literature; most clinical features did not distinguish significantly between viral, atypical, or bacterial pneumonia [6, 20, 22, 27]. Only the presence of hypoxemia at inclusion was significantly associated with viral etiology. Age-related tachypnea, a cornerstone in the WHO clinical case definition, did not predict radiological confirmed CAP, a finding consistent with other studies [16, 34, 35, 41]. Perhaps more surprisingly in our cohort, wheeze was equally prevalent across etiological and radiological categories and hence not associated with either of our outcomes. This is in contrast to previous studies, finding wheeze as a negative predictor of positive chest radiography in suspected CAP [30] and associated with viral CAP by others [29]. The new

epidemiological situation with a large impact of viral infections may explain wheeze's lack of predictive ability, and the relatively high proportion of bacterial-viral co-infection may additionally obscure its predictive ability in differentiating etiology. Fever has been reported as the most consistent clinical feature in pediatric CAP [8]. In our study, fever ≥38.5 °C was a common finding but not significantly associated with etiology or radiographic findings in either univariate or multivariate analyses. Previous studies have found older age to be associated with bacterial CAP [9, 22], but in our study only associated with atypical pneumonia.

A major strength of this study is that both clinical features and laboratory findings are first analyzed in suspected and then in proven CAP cases. By this two-step approach, we simulate the diagnostic approach in the pediatric emergency room. The findings reported here should reflect the epidemiology of pediatric CAP in our and socio-demographically similar regions. With few bacterial pneumonia cases and few school-aged children with pneumonia, conclusions in these groups must be interpreted cautiously. Furthermore, and as discussed in our previous publication [2], there are several obstacles in the microbiological diagnosis of pneumonia, introducing some uncertainty in our etiological classification and hence influencing the ability of clinical and laboratory features in predicting etiology. On the other hand, the validity of our etiological results is corroborated by similar results in a recent, large US multicenter CAP study [19]. We believe that combining a variety of univariate and multivariate statistical analyses makes our findings more robust. The present study includes patients at all treatment levels including primary care, increasing the usefulness of our study for clinical decisions concerning admission and antibiotic use. Caution should be taken, however, when making direct comparison to CAP studies of only hospitalized patients. In order to make an easily communicable pneumonia definition, intention to treat with antibiotics for suspected pneumonia in primary care was set as an inclusion criterion in these patients. This may have lead to selection bias compared to patients included by hospital pediatricians. Measurements of clinical features were done by staff on call, and although all staff there are trained in these routine measurements, we cannot exclude errors in data collection. Due to the lack of a uniform clinical definition [27], comparison with other studies may also be hampered as pneumonia definition varies. Our approach in only assigning

radiographic findings seen by both radiologists as positive to reduce interrater variability and increase specificity may have been at the cost of reduced sensitivity. Our low proportion of interstitial infiltrates may reflect this. Our one-center setting is a limitation, and representativeness must be kept in mind when applying our results to socio-demographically similar populations.

In conclusion, in this study of pediatric pneumonia in a population with a high coverage of pneumococcal vaccination, clinical features are of little diagnostic value, in accordance with previous studies. An exception is reduced peripheral oxygen saturation at admission, which is predictive of viral etiology. Elevated CRP and WBC counts gave relatively high specificity and positive likelihood ratios and may thus be beneficial in (i) ruling in positive chest radiography in suspected CAP and (ii) ruling in bacterial etiology in radiological proven CAP. Although poor sensitivity, and a relatively low but significant OR for CRP, reduces their clinical usefulness, our findings may contribute to reductions in antibiotic and chest radiography use in resource-rich settings with good routine immunization programs. In cases with low CRP and low white blood cell counts, a watch-and-wait strategy in children with suspected or proven pneumonia may be applied without detrimental effects.

## Acknowledgements

We are grateful to all participating children and their parents and nurses and doctors on call for recruiting patients and collecting data. We thank Drs. R Bull and R Grotli at the Department for Radiology, Akershus University Hospital, for performing the radiological examinations; Dr. I Aaberge and A Aase for the pneumococcal serological analyses at the Department of Bacteriology and Immunology, the Norwegian Institute for Public Health; and Dr. Line Sletner at our department for the advise on statistical analyses and staff at the laboratories at Akershus University Hospital for performing the laboratory analyses.

*Authors' contributions* All authors provided substantial contributions to the study's conception and design and acquisition, analysis, or interpretation of the data.

Drs. Berg, Inchley, Fjaerli, and Nakstad executed the clinical part of the work.

Dr. Leegaard was responsible for the microbiological laboratory analyses.

Dr. Lindbaek was responsible for the primary care part of the study.

Dr. Berg drafted the initial manuscript, and all other authors revised it critically for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

### Compliance with ethical standards

*Conflict of interest* The authors declare that they have no conflicts of interest.

*Ethical approval* All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and approved by both the Regional Ethics Committee and the local Data Protection Officer. Furthermore, the study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

*Informed consent* Informed consent was obtained from all individual participants included in the study.

*Source of funding* The study was supported by research grants from Akershus University Hospital and South-Eastern Norway Regional Health Authority and grants from the Grimsgaard Foundation and the Norwegian Organization for Surveillance of Antimicrobial Resistance.

## References

1. Angoulvant F, Levy C, Grimprel E, Varon E, Lorrot M, Biscardi S, Minodier P, Dommergues MA, Hees L, Gillet Y, Craiu I, Zenkhri F, Dubos F, Guen CG, Launay E, Martinot A, Cohen R (2014) Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. Clin Infect Dis 58(7):918–924. doi: 10.1093/cid/ciu006

2. Berg AS, Inchley CS, Aase A, Fjaerli HO, Bull R, Aaberge I, Leegaard TM, Nakstad B (2016a) Etiology of pneumonia in a pediatric population with high pneumococcal vaccine coverage: a prospective study. Pediatr

Infect Dis J 35(3):e69–e75. doi: 10.1097/INF.0000000000001009

3. Berg AS, Inchley CS, Fjaerli HO, Leegaard TM, Nakstad B (2016b) Microbial aetiology of paediatric pneumonia complicated with parapneumonic effusion in the era of pneumococcal vaccination. Infect Dis (Lond) 48(9):712–714. doi: 10.1080/23744235.2016.1192721

4. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH Jr, Moore MR, St Peter SD, Stockwell JA, Swanson JT, Pediatric Infectious Diseases S, the Infectious Diseases Society of A (2011) 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 53(7):e25–e76. doi: 10.1093/cid/cir531

5. Cherian T, Mulholland EK, Carlin JB, Ostensen H, Amin R, de Campo M, Greenberg D, Lagos R, Lucero M, Madhi SA, O'Brien KL, Obaro S, Steinhoff MC (2005) Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ 83(5):353–359

6. Chiappini E, Venturini E, Galli L, Novelli V, de Martino M (2013) Diagnostic features of community-acquired pneumonia in children: what's new? Acta Paediatr Suppl 102(465):17–24. doi: 10.1111/apa.12502

7. Craig JC, Williams GJ, Jones M, Codarini M, Macaskill P, Hayen A, Irwig L, Fitzgerald DA, Isaacs D, McCaskill M (2010) The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. BMJ 340:c1594. doi: 10.1136/bmj.c1594

8. Don M, Canciani M, Korppi M (2010) Community-acquired pneumonia in children: what's old? What's new? Acta Paediatr 99(11):1602–1608. doi: 10.1111/j.1651-2227.2010.01924.x

9. Elemraid MA, Rushton SP, Thomas MF, Spencer DA, Gennery AR, Clark JE (2014) Utility of inflammatory markers in predicting the aetiology of

pneumonia in children. Diagn Microbiol Infect Dis 79(4):458–462. doi: 10.1016/j.diagmicrobio.2014.04.006

10. Esposito S, Bosis S, Cavagna R, Faelli N, Begliatti E, Marchisio P, Blasi F, Bianchi C, Principi N (2002) Characteristics of *Streptococcus pneumoniae* and atypical bacterial infections in children 2–5 years of age with community-acquired pneumonia. Clin Infect Dis 35(11):1345–1352. doi: 10.1086/344191

11. Flood RG, Badik J, Aronoff SC (2008) The utility of serum C-reactive protein in differentiating bacterial from nonbacterial pneumonia in children: a meta-analysis of 1230 children. Pediatr Infect Dis J 27(2):95–99. doi: 10.1097/INF.0b013e318157aced

12. Galetto-Lacour A, Alcoba G, Posfay-Barbe KM, Cevey-Macherel M, Gehri M, Ochs MM, Brookes RH, Siegrist CA, Gervaix A (2013) Elevated inflammatory markers combined with positive pneumococcal urinary antigen are a good predictor of pneumococcal community-acquired pneumonia in children. Pediatr Infect Dis J 32(11):1175–1179. doi: 10.1097/INF.0b013e31829ba62a

13. Gove S (1997) 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 75(Suppl 1):7–24

14. Harnden A, Perera R, Brueggemann AB, Mayon-White R, Crook DW, Thomson A, Mant D (2007) Respiratory infections for which general practitioners consider prescribing an antibiotic: a prospective study. Arch Dis Child 92(7):594–597. doi: 10.1136/adc.2007.116665

15. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, Thomson A (2011) British Thoracic Society guidelines for the management of community acquired pneumonia in children: update. Thorax 66(Suppl 2):ii1–i23. doi: 10.1136/thoraxjnl-2011-200598

16. Hazir T, Nisar YB, Qazi SA, Khan SF, Raza M, Zameer S, Masood SA

(2006) Chest radiography in children aged 2–59 months diagnosed with non-severe pneumonia as defined by World Health Organization: descriptive multicentre study in Pakistan. BMJ 333(7569):629. doi: 10.1136/bmj.38915.673322.80

17. Heiskanen-Kosma T, Korppi M (2000) Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare settings. Scand J Infect Dis 32(4):399–402

18. Hinchliffe R (1992) Reference values. In: Lilleyman J, Hann I (eds) Pediatric hematology, 2nd edn. Churchill Livingstone, Edinburgh, pp 1–22

19. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, Stockmann C, Anderson EJ, Grijalva CG, Self WH, Zhu Y, Patel A, Hymas W, Chappell JD, Kaufman RA, Kan JH, Dansie D, Lenny N, Hillyard DR, Haynes LM, Levine M, Lindstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, Wunderink RG, Edwards KM, Pavia AT, McCullers JA, Finelli L, Team CES (2015) Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 372(9):835–845. doi: 10.1056/NEJMoa1405870

20. Juven T, Mertsola J, Toikka P, Virkki R, Leinonen M, Ruuskanen O (2001) Clinical profile of serologically diagnosed pneumococcal pneumonia. Pediatr Infect Dis J 20(11):1028–1033

21. Korppi M, Heiskanen-Kosma T, Leinonen M (1997) White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. Eur Respir J 10(5):1125–1129

22. Korppi M, Don M, Valent F, Canciani M (2008) The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. Acta Paediatr 97(7):943–947. doi: 10.1111/j.1651-2227.2008.00789.x

23. Koster MJ, Broekhuizen BD, Minnaard MC, Balemans WA, Hopstaken RM, de Jong PA, Verheij TJ (2013) Diagnostic properties of C-reactive protein for detecting pneumonia in children. Respir Med 107(7):1087–1093.

doi: 10.1016/j.rmed.2013.04.012

24. Lowell DI, Lister G, Von Koss H, McCarthy P (1987) Wheezing in infants: the response to epinephrine. Pediatrics 79(6):939–945

25. Lynch T, Platt R, Gouin S, Larson C, Patenaude Y (2004) Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? Pediatrics 113(3 Pt 1):e186–e189

26. Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, Donnelly LF, Bracey SE, Duma EM, Mallory ML, Slap GB (2005) Identifying children with pneumonia in the emergency department. Clin Pediatr (Phila) 44(5):427–435

27. McIntosh K (2002) Community-acquired pneumonia in children. N Engl J Med 346(6):429–437. doi: 10.1056/NEJMra011994

28. van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ (2005) Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ 331(7507):26. doi: 10.1136/bmj.38483.478183.EB

29. Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, Kauppila J, Leinonen M, McCracken GH Jr (2004) Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 113(4):701–707

30. Neuman MI, Monuteaux MC, Scully KJ, Bachur RG (2011) Prediction of pneumonia in a pediatric emergency department. Pediatrics 128(2):246–253. doi: 10.1542/peds.2010-3367

31. Oostenbrink R, Thompson M, Lakhanpaul M, Steyerberg EW, Coad N, Moll HA (2013) Children with fever and cough at emergency care: diagnostic accuracy of a clinical model to identify children at low risk of pneumonia. Eur J Emerg Med 20(4):273–280. doi: 10.1097/MEJ.0b013e32835771fd

32. Prat C, Dominguez J, Rodrigo C, Gimenez M, Azuara M, Jimenez O, Gali N, Ausina V (2003) Procalcitonin, C-reactive protein and leukocyte count in children with lower respiratory tract infection. Pediatr Infect Dis J 22(11):963–968. doi: 10.1097/01.inf.0000095197.72976.4f

33. Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V (2015) Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. Lancet Infect Dis 15(4):439–450. doi: 10.1016/s1473-3099(15)70017-4

34. Rothrock SG, Green SM, Fanelli JM, Cruzen E, Costanzo KA, Pagane J (2001) Do published guidelines predict pneumonia in children presenting to an urban ED? Pediatr Emerg Care 17(4):240–243

35. Shah S, Bachur R, Kim D, Neuman MI (2010) Lack of predictive value of tachypnea in the diagnosis of pneumonia in children. Pediatr Infect Dis J 29(5):406–409. doi: 10.1097/INF.0b013e3181cb45a7

36. Solevag AL, Eggen EH, Schroder J, Nakstad B (2013) Use of a modified pediatric early warning score in a department of pediatric and adolescent medicine. PLoS One 8(8):e72534. doi: 10.1371/journal.pone.0072534

37. Toikka P, Irjala K, Juven T, Virkki R, Mertsola J, Leinonen M, Ruuskanen O (2000) Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. Pediatr Infect Dis J 19(7):598–602

38. Trogstad L, Ung G, Hagerup-Jenssen M, Cappelen I, Haugen IL, Feiring B (2012) The Norwegian immunisation register—SYSVAK. Euro Surveill 17 (16)

39. Van den Bruel A, Thompson MJ, Haj-Hassan T, Stevens R, Moll H, Lakhanpaul M, Mant D (2011) Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ 342:d3082. doi: 10.1136/bmj.d3082

40. Virkki R, Juven T, Rikalainen H, Svedstrom E, Mertsola J, Ruuskanen O

(2002) Differentiation of bacterial and viral pneumonia in children. Thorax 57(5):438–441

41. Wingerter SL, Bachur RG, Monuteaux MC, Neuman MI (2012) Application of the world health organization criteria to predict radiographic pneumonia in a US-based pediatric emergency department. Pediatr Infect Dis J 31(6):561–564. doi: 10.1097/INF.0b013e31824da716