

# Occult Pneumonia in Infants With High Fever Without Source

## A Prospective Multicenter Study

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**Background:** The prevalence of pneumonia in infants with high fever without source (FWS; temperature,  $\geq 39.0^{\circ}\text{C}$ ) and a white blood cell (WBC) count greater than  $20 \times 10^9/\text{L}$  (occult pneumonia) has been reported to be 20% before the introduction of the 7-valent pneumococcal conjugated vaccine (PCV7). This is the main reason for carrying out chest x-ray (CXR) on infants with high FWS. The aims of this study were to establish the prevalence of occult pneumonia in well-appearing infants with high FWS (temperature,  $\geq 39.0^{\circ}\text{C}$ ) and a WBC count greater than  $20 \times 10^9/\text{L}$  in the era of PCV7 and to analyze the value of WBC, absolute neutrophil count (ANC), and C-reactive protein (CRP) level as predictors of the risk of occult pneumonia in these patients.

**Patients and Methods:** We conducted a multicenter prospective study in 4 pediatric emergency departments including children younger than 36 months with FWS (temperature,  $\geq 39.0^{\circ}\text{C}$ ) and a WBC count higher than  $20 \times 10^9/\text{L}$  on whom a CXR was performed in the absence of respiratory findings. Physicians completed a questionnaire when observing the infant, and the attending physician or, when in doubt, the radiologist interpreted the CXR. Multivariable binary logistic regression was used to estimate the adjusted relative influences of the aforementioned factors on the prevalence of radiological pneumonia.

**Results:** During an entire year (September 2006 to September 2007), we included 188 infants (aged 1–36 months; 56.2% were males) with high FWS and a WBC count greater than  $20 \times 10^9/\text{L}$  (range,  $20\text{--}44.7 \times 10^9/\text{L}$ ) on whom a CXR was performed. Of the 188 chest radiographs obtained, 37 (19.7%) were interpreted by the radiologist. Consolidation in the chest radiographs was detected in 25 (13.3%). The probability of an infant with high FWS and WBC of  $20 \times 10^9/\text{L}$  or greater having pneumonia was related to 3 of the studied variables: age, ANC, and serum CRP level.

The incidence of pneumonia increased with age (odds ratio [OR] of 2.62 for infants  $>12$  months; 95% confidence interval [95% CI], 1.04–6.60), CRP level greater than 100 mg/L (OR, 3.18; 95% CI, 1.19–8.51), and ANC greater than  $20 \times 10^9/\text{L}$  (OR, 3.52; 95% CI, 1.37–9.06).

White blood cell count was not predictive of occult pneumonia when ANC was taken into account.

**Conclusions:** In the era of PCV7, the incidence of pneumonia in infants younger than 36 months with high FWS and WBC count greater than  $20 \times 10^9/\text{L}$  seems to be lower than that previously reported. However, this is not a uniform group because the incidence of pneumonia increases in infants older than 12 months and with higher ANC and serum CRP level.

**Key Words:** pneumonia, fever, infants, leukocytosis

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Fever is one of the most common reasons for visiting the pediatric emergency department (ED). In our environment, 3% to 4% of annual consultations correspond to children younger than 3 years with fever but without focal signs of infection.<sup>1</sup>

Although most febrile children who present to the ED are presumed to have a viral illness, some children with fever and no apparent source on physical examination (fever without source, FWS) may have serious bacterial infections (SBIs). These SBIs are more common in young children with high FWS, and moreover, in these patients, it is more difficult to distinguish those with simple viral illness from those with an SBI; therefore, the risk of occult bacteremia is higher. After initial medical history and physical examination of a febrile infant, the physician must decide whether to perform any tests designed to look for occult infections and how the results of the tests will influence the child's treatment (prompting more tests, a change in therapy, and/or an alteration in follow-up). Diagnostic testing tends to be more extensive in young children with high fever and no identifiable infectious source. In this way, the white blood cell (WBC) count is used by many physicians to screen febrile children for underlying bacterial infection, especially those who are young and have a very high temperature, prolonged fever, or no localizing signs of infection. White blood cell counts have been recommended in young children with high fever as part of their diagnostic screening. The clinician faced with an increased WBC count must then decide on further diagnostic tests and on whether to administer empiric antibiotic therapy.

The diagnostic tests often considered after an increased WBC count is noted include blood culture, urinalysis ( $\pm$  urine culture), and chest x-ray (CXR).

Chest radiographies do not play a role in the routine evaluation of the infant with FWS.<sup>2–4</sup> However, in 1999, Bachur et al<sup>5</sup> concluded that empiric CXRs in highly febrile children with leukocytosis and no findings of pneumonia frequently reveal occult pneumonias. Following the authors' recommendations, CXR should be considered a routine diagnostic test in children with a temperature of  $39^{\circ}\text{C}$  or higher and a WBC count of  $20 \times 10^9/\text{L}$  or greater without an alternative major source of infection. Approximately 20% of these patients will have an occult pneumonia.

The introduction of the 7-valent pneumococcal conjugated vaccine (PCV7) has decreased the incidence of invasive pneumococcal infections and has changed the approach to young febrile children with FWS. Notably, physicians are ordering fewer WBC counts,<sup>6,7</sup> although the impact of PCV7 on the prevalence of occult pneumonia remains unknown.<sup>8</sup>

Serum C-reactive protein (CRP) has been evaluated as a predictor of SBI in young febrile children,<sup>9</sup> and in a recent study, it was reported to weakly predict a bacterial etiology.<sup>10</sup>

The aims of this study were to establish the incidence of pneumonia in well-appearing infants with high FWS (temperature,  $\geq 39.0^{\circ}\text{C}$ ) and a WBC count higher than  $20 \times 10^9/\text{L}$  (occult pneumonia) in the era of PCV7 and to analyze the value of WBC, absolute neutrophil count (ANC), and CRP level as predictors of the risk of occult pneumonia in these patients.

**PATIENTS AND METHODS**

We carried out a multicenter prospective study during an entire year in 4 pediatric EDs in different regions in Spain (2 in Basque Country and 1 each in Madrid and in Catalonia) attending around 250,000 patient visits to the ED annually. In these 4 EDs, the policy is to carry out a CXR on infants younger than 36 months with high fever ( $>39^{\circ}\text{C}$ ) and a WBC count higher than  $20 \times 10^9/\text{L}$ .

- Inclusion criteria were as follows:
  - Be younger than 36 months.
  - Be well appearing as assessed by a pediatric emergency faculty physician. A child was defined as well appearing if result of the Pediatric Assessment Triangle of the Advanced Pediatric Life Support was normal.
  - Be without catarrhal or respiratory symptoms/signs (such as tachypnea) or a diarrheal process in a patient with a normal physical examination result (no signs of acute otitis media, osteoarticular or soft tissue infection, and normal pulmonary auscultation).
  - Have a complete blood cell (CBC) count and blood culture as part of their evaluation for fever and a WBC count greater than  $20 \times 10^9/\text{L}$ .
- Excluded were as follows:
  - Infants who were not well appearing as reflected in the patient chart.
  - Children with immunodeficiency.
  - Patients in whom the anamnesis and/or the physical examination allowed for identification of the origin of the fever, specifically children diagnosed, according to the diagnosis coding of the Spanish Society of Pediatric Emergencies, with upper respiratory tract infection or acute gastroenteritis.
  - Patients who were taking antibiotics before presenting to the ED.

Physicians completed a questionnaire with each patient indicating sociodemographic data, duration and level of fever, absence of respiratory symptoms (cough, congestion, breathing difficulty, and wheezing), absence of respiratory signs (nasal congestion, observed cough, tachypnea, grunting, nasal flaring, retractions, snoring, wheezing, rales, and focal area of decreased breath sounds), tests carried out on the patient, and their results, diagnosis, destination, and treatment administered.

In order for a patient to be included in the study, the attending physician had to affirmatively answer the following question: Do I perform the CXR exclusively because of age and WBC count higher than  $20 \times 10^9/\text{L}$  in the absence of respiratory symptoms/signs?

Pneumonia was defined by the report of the attending pediatrician and, when in doubt, by the emergency radiologist.

Pneumonia was defined as radiology findings of consolidation or infiltrate(s) reported in definite terms; these patients were considered to have an occult pneumonia.

To avoid seasonal variation, data were collected for an entire year.

Questionnaires were sent to the main investigator (S.M., Cruces Hospital) who was responsible for statistical analysis.

**Statistical Analysis**

Data were expressed as mean and SD for quantitative variables or numbers and percentages for categorical variables. Variables hypothesized to be predictive of occult pneumonia were categorized as age younger or older than 12 months, WBC count lower or higher than  $30 \times 10^9/\text{L}$ , ANC lower or higher than  $20 \times 10^9/\text{L}$ , and CRP level lower or higher than 100 mg/L, to reproduce categories commonly used in our clinical practice to guide test ordering and therapeutical decisions. A multivariable binary logistic regression model was fitted, and likelihood ratio tests were used to select significant predictors. The program SPSS 15.0 for Windows (SPSS, Inc, Chicago, Ill) was used for all statistical calculations. Statistical significance was defined as  $P < 0.05$ .

**RESULTS**

We included 188 infants younger than 36 months (age range, 1–36 months; 55.9% were males) for 12 consecutive months beginning September 1, 2006, with high FWS (temperature of  $\geq 39.0^{\circ}\text{C}$  registered at home and/or at triage) and a WBC count of  $20 \times 10^9/\text{L}$  or greater (range,  $20\text{--}44.7 \times 10^9/\text{L}$ ) on whom a CXR was performed. Of the 188 CXRs carried out, 37 (19.7%) were interpreted by the radiologist.

Tests carried out on these patients can be seen in Table 1. In 7 patients (3.7%), a pneumococcus was isolated in the blood culture (1 infant with pneumonia [4%] and 6 patients with normal chest radiograph result [3.6%]).

Consolidation in the chest radiographs was detected in 25 patients (13.3%; 95% confidence interval [95% CI], 9.2%–18.9%).

The probability of an infant with high FWS and a WBC count of  $20 \times 10^9/\text{L}$  or greater having pneumonia was not uniform and was related to 3 of the variables studied: age, ANC, and serum CRP level. In this way, the incidence of pneumonia increased significantly in infants older than 12 months (odds ratio [OR] of 2.62 for infants older than 12 months; 95% CI, 1.04–6.60), with CRP level greater than 100 mg/L (OR, 3.18; 95% CI, 1.19–8.51), and ANC greater than  $20 \times 10^9/\text{L}$  (OR, 3.52; 95% CI, 1.37–9.06). In contrast, WBC count was not predictive of occult pneumonia when ANC was taken into account (Table 2).

A simple flowchart based on the objective data can help identify patients at greater risk of occult pneumonia (Fig. 1).

**DISCUSSION**

According to the data of our multicenter prospective study, in the era of PCV, the incidence of pneumonia in infants younger than 36 months with high FWS ( $>39^{\circ}\text{C}$ ) and a WBC count greater than  $20 \times 10^9/\text{L}$  is around 13%, and the likelihood of

**TABLE 1. Tests Carried Out**

	n	%
CXR	188	100
CBC count	188	100
Blood culture	188	100
Serum CRP	188	100
Urine dipstick	165	87.7
Urine culture	127	67.5
CSF culture	42	22.3

**TABLE 2.** Percentage of Patients With Occult Pneumonia Related With Historical and Laboratory Features

Feature	% of Patients With Occult Pneumonia	OR* (95% CI)	Adjusted OR* (95% CI)
Age, mo			
>12	21.9	3.31 (1.28–8.71)	2.62 (1.04–6.60)
<12	7.8		
White blood cell count, $\times 10^9/L$			
>30	21.9	2.15 (0.73–6.19)	*
$\leq 30$	11.5		
ANC, $\times 10^9/L$			
>20	30.6	4.34 (1.62–11.64)	3.52 (1.37–9.06)
$\leq 20$	9.2		
CRP, mg/L			
>100	28.1	3.42 (1.23–9.48)	3.18 (1.19–8.51)
$\leq 100$	10.3		

\*The regression model used to estimate OR included age (2 categories), CRP level (2 categories), and ANC (2 categories). White blood cell was not used because it was not significantly associated with occult pneumonia.

having an occult pneumonia is related to age, ANC, and serum CRP level.

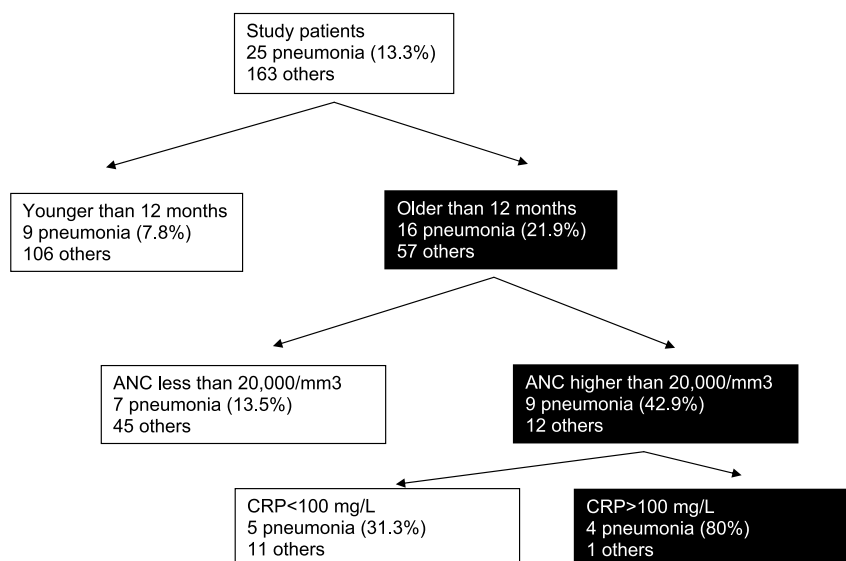
Chest radiographies do not seem to play a role in the routine evaluation of the infant with FWS.<sup>2–4,11</sup> Bachur et al<sup>5</sup> suggested in 1999 that CXR should be considered a routine diagnostic test in selected infants. They found a 20% prevalence of occult pneumonia in highly febrile children without an alternative major source of infection and a WBC count of  $20 \times 10^9/L$  or greater.

Recently, Murphy et al<sup>12</sup> reported occult pneumonia in 5.3% of patients aged 10 years or younger with fever and no lower respiratory tract findings, tachypnea, or respiratory distress. The incidence of pneumonia in patients with a WBC count greater than  $20 \times 10^9/L$  was 12.3%. This was a retrospective study analyzing physician records of ED patients aged 10 years or younger who presented with fever (38°C) and underwent a CXR for suspected pneumonia.

To our knowledge, except for the study of Murphy et al,<sup>12</sup> in recent years, there has been no study on the incidence of

occult pneumonia in these infants, although the introduction of PCV7 has decreased the incidence of invasive pneumococcal infections, and it has been suggested that PCV7 may play an important role in reducing the burden of pneumonia in the United States.<sup>13</sup> The PCV7 was introduced in Spain in 2001 and resulted in a decline in the rate of *Streptococcus pneumoniae* occult bacteremia in our area, attributable to a decrease in the rate of disease caused by PCV7 serotypes as had been broadly reported in the United States.<sup>14</sup> This decline has altered the recommendations for the management of infants with FWS.<sup>7</sup>

In Spain, although available since 2001, to date, the PCV7 has not been included in the official vaccination schedule of the public health system, except in Madrid. This is one of the reasons that use of PCV7 in the various Spanish regions is irregular, when one attends to the percentage of vaccinated children presenting to Spanish EDs. The percentage of children who had received at least 1 dose of PCV7 varied according to the different geographical areas (33%–49% of patients



**FIGURE 1.** Rate of occult pneumonia related to age, absolute neutrophil count and C-reactive protein.

visiting our pediatric EDs), and hence, the incidence of occult pneumonia may be differentially related to current vaccination rates.<sup>15</sup>

The PCV7 has been associated with a dramatic decrease in invasive pneumococcal infections, although the impact on the prevalence of occult pneumonia has remained unknown.<sup>8</sup> Recently, Zhou et al<sup>13</sup> analyzed health care visits for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States, with the objective of estimating the effect of PCV7 on rates of pneumonia-related health care utilization and costs for children younger than 2 years. Zhou et al<sup>13</sup> concluded that in children younger than 2 years, pneumonia-related health care utilization in a privately insured population declined substantially after the introduction of PCV7. These results suggest that PCV7 may play an important role in reducing the burden of pneumonia, resulting in major savings in medical care costs. In a similar manner, Grijalva et al<sup>16</sup> recently reported that at the end of 2004, all-cause pneumonia admission rates in the United States had declined by 39% for children younger than 2 years—the target population of the PCV7 vaccination program. This decrease represented approximately 41,000 pneumonia admissions prevented in that year alone.

With the advent of widespread PCV7 use, the practice of evaluating children for occult bacteremia is declining,<sup>7</sup> and the frequency in which a WBC count is obtained has also declined. Nevertheless, the fact that native Alaskan children are experiencing replacement invasive pneumococcal disease with serotypes not covered by heptavalent pneumococcal conjugate vaccine highlights the importance of ongoing surveillance and development of expanded valency vaccines.<sup>17</sup> However, infants with leukocytosis will probably remain a challenge for the pediatric emergency physician, and our study may help to identify those at greatest risk for occult pneumonia.

Our study specifically looks for pneumonia in infants younger than 36 months in whom a WBC count is taken in the evaluation of the fever. According to our study, in the era of PCV, the incidence of occult pneumonia in infants less than 36 months of age with high FWS and a WBC count higher than  $20 \times 10^9/L$  is around 13%, and the likelihood of having an occult pneumonia is related to age, ANC, and serum CRP level.

There is no single reliable predictor of serious infections in infants. White blood cell is universally available and historically useful as an indicator of serious infections. However, although WBC is traditionally used as an indicator of serious infection, it has been shown to be an ineffective single tool, overshadowed by newer indicators such as CRP and procalcitonin levels. Recent research has identified CRP and procalcitonin levels as 2 new useful tools in the battery of tests available to investigate the cause of fever in infants and children. Procalcitonin and CRP levels perform better than WBC count and ANC in predicting serious infections in children with FWS.<sup>18–21</sup> Along these lines, in our study, CRP level seems to be useful as a predictor of the risk of occult pneumonia in selected infants with high FWS. An ideal biomarker for pneumonia should allow an early differential diagnosis from non-infectious conditions and should inform about the course and prognosis of the disease. Procalcitonin covers these features better than the more commonly used biomarkers like CRP or leukocyte count.<sup>22,23</sup>

Our study has several limitations. The body temperature used to include patients for our analysis was the temperature recorded at home or at triage and not the temperature recorded in the pediatric ED. The indications for obtaining (or not

obtaining) a CBC count were not analyzed. Interpretations of the chest radiographs were not always by a radiologist, and this fact may have altered the interpretation of it. It would have been better to have had an independent analysis by a pediatric radiologist according to predetermined criteria and blind to the child's condition. However, all the CXRs carried out were interpreted by at least one experienced pediatric emergency physician.

In the era of PCV7, management of young children with FWS remains challenging for the pediatric emergency physician. Ongoing surveillance of the value of different old and new tests carried out on these children seems to be needed to adjust the approach in the pediatric ED.

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