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RESEARCH PAPER

Absence of leukocytosis in bacteraemic pneumococcal pneumonia

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Abstract

Background: Evaluation of patients with respiratory symptoms in primary care medicine is often based on peripheral WBC count that dictates the extent of diagnostic investigation. A normal WBC count may result in a limited investigation, often omitting chest radiography.

Aims: To determine the extent to which patients hospitalised with bacteraemic pneumococcal pneumonia have no leukocytosis at presentation.

Methods: A retrospective analysis was performed of patients with bacteraemic community-acquired pneumococcal pneumonia from 2000 to 2007 in a community care academic medical centre. Records were reviewed for symptoms, signs, and laboratory data including pneumococcal serotypes, chest radiographs on admission, and outcome.

Results: 21% of the patients presented with a normal WBC count (16.7% of the children and 25.6% of the adults). Among this population with a normal WBC count at presentation, 90% of the adults and 70% of the children developed leukocytosis within a few days after admission.

Conclusions: In this study, in as many as one-fifth of all the patients with bacteraemic pneumococcal pneumonia, there was no leukocytosis at presentation. We therefore suggest that every patient with clinically suspected pneumonia should undergo chest radiography even if the WBC count is normal.

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Introduction

Community-acquired pneumonia (CAP) is a common and serious illness with considerable morbidity and mortality.[1] An estimated 5.6 million cases of CAP occur annually in the United States,[2] with 1.2 million patients hospitalised and an inpatient mortality rate of 5.8%.[3] *Streptococcus pneumoniae* accounts for about 50% of all cases of CAP requiring admission to hospital.[4] Diagnostic evaluation of patients with symptoms suggestive of pneumonia is important and quite common, especially in the primary care setting. Since the presenting symptoms are often non-specific, the accurate assessment leading to a diagnosis of CAP should be pursued and followed by the appropriate assessment of illness severity. The diagnosis of CAP is suggested by the presence of non-specific clinical features (e.g. cough, fever, purulent sputum, and sometimes pleuritic chest pain) along with auscultatory findings, and is confirmed by imaging of the lungs, usually by chest radiography.[5,6] Current clinical practice is still frequently based on the peripheral white blood cell (WBC) count in evaluating patients presenting with respiratory symptoms. While a finding of leukocytosis prompts a physician to obtain a chest radiograph, a normal WBC count supports a less extensive investigation, often omitting chest radiography, sending serology for atypical pneumonia, and even starting inappropriate treatment.

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In patients with pneumococcal pneumonia the peripheral WBC count generally exceeds 11,000/mm^3,[7,8] although it can be lower than 6,000/mm^3 in 5–10% of patients. Such a low count has been found to be strongly associated with a poor prognosis.[8–10]

It is not known what proportion of patients with bacteraemic pneumococcal pneumonia present with a normal WBC count and thus might have a deferred or incorrect diagnosis and treatment.

The aim of this study was to determine the percentage of inpatients with bacteraemic pneumococcal CAP presenting without leukocytosis to an emergency department and to characterise this group of patients.

Methods

Study subjects and data collection

The study was retrospectively conducted in a 550-bed community care university hospital. The charts of all patients discharged with diagnoses of 'pneumococcal pneumonia' (ICD code 481) or 'pneumonia and pneumococcal bacteremia' (ICD codes 486 and 041.2) from 1 January 2000 to 31 December 2007 were reviewed.

Community-acquired pneumococcal pneumonia was defined as symptoms of the lower respiratory tract along with new infiltrates seen on a chest radiograph and the presence of blood culture-proven pneumococcal infection. Exclusion criteria were immunocompromised patients, haematological or oncological disease and systemic steroid treatment.

The following data were collected: demographic characteristics, pre-existing co-morbid medical conditions, smoking status, initial vital signs, routine laboratory test results, pneumococcal serotypes isolated from blood cultures, and outcome of the hospitalisation with special mention of ventilation. The pneumonia severity index was calculated according to Patient Outcome Research Team (PORT) criteria for all adult patients.[11]

According to our laboratory reference values, leukocytosis was defined as ≥10,000 cells/mm^3. For the purpose of this study, mild leukocytosis was defined as 10,000-15,000 cells/mm^3, significant leukocytosis as 15,000-25,000 cells/mm^3, and extreme leukocytosis (leukaemoid reaction) as ≥25,000 cells/mm^3.

Approval from the Institutional Review Board was waived as this was a retrospective study with chart analysis.

Statistical analysis

Data were typed into an Excel spreadsheet (Microsoft, USA) and analysed by EpiInfo 3.5.1 (CDC, Atlanta, USA); Stata 9.0 (StataCorp, Texas, USA) was used for logistic regression analysis. We applied the χ^2 test (Fisher exact test where applicable) for categorical variables and the two-tailed non-paired t test for continuous variables.

For the purpose of our analysis, children were defined as subjects <18 years of age and adults were defined as subjects ≥18 years of age.

Results

During an 8-year period, 120 patients with encoded diagnoses of 'pneumococcal bacteremia' (ICD code 041.2) and 'pneumonia' (ICD code 486) (n=17) or 'pneumococcal pneumonia' (ICD code 481) (n=103) were identified in our computerised hospital's diagnosis data. After reviewing the charts, 39 cases were excluded: 35 failed to meet the established diagnostic inclusion criteria due to either erroneous coding or an absence of blood culture-proven pneumococcal bacteraemia and four had an underlying malignancy. No patients were immunosuppressed or on steroid treatment. Thus, 81 patients with bacteraemic pneumococcal pneumonia were included in the study. There were no nosocomial cases.

The baseline characteristics of the patient population are presented in Table 1.

All children and the majority (80%) of the adults were non-smokers. In the adult group, 20% of patients were current smokers, 10% reported smoking in the past, and in 10% the smoking status was not reported. Almost 30% of the children were treated with antibiotics prior to hospitalisation compared with 2.5% of the adults.

The mean PORT score at admission was calculated in the entire adult group except for one case in which some data were unavailable. No cases were in PORT class I as these patients are usually treated on an outpatient basis; 33% of patients were in the lower PORT scale (II and III) while the majority (70%) were in classes IV and V. Seven patients (8.6%) died during hospitalisation, all of whom were adults. In these cases the PORT score on admission ranged from 138 to 219 (class V). The mean±SD hospital stay was 6.0±4.6 days for children and 10.6±12.6 for adults.

As anticipated, higher rates of co-morbidities were found in adults than in children. Three children had heart failure: two cases were associated with atrioventricular canal defects (in patients with Down syndrome) and one case with atrial septal defect (Holt Oram syndrome). Lung disease was detected in four subjects, two of whom were the aforementioned patients (one with Down syndrome and the other with Holt Oram syndrome), while the two others had asthma. The hospital course was complicated with empyema and drainage in eight children and four adults. Three of the eight children and one of the four adults with empyema had a normal WBC count at presentation. They all developed a high WBC count during their hospitalisation course. The maximal WBC count developed in children with empyema without leukocytosis at presentation at 4.7±0.6 days and in adults with empyema at 7±0 days after admission. The average hospital stay in patients with empyema was

Table 1. Baseline characteristics of the patient population*

	Children (<18 yrs)	Adults (≥18 yrs)
Number	42	39
Mean age (years)	2.4±2.2	55.8±23.2
Age range (years)	0.4–9	21–94
Male sex (%)	54.8	53.9
Smoker (%)	0	20.1
Past smoker (%)	0	10.2
Previous antibiotic use (%)	28.6	2. 6
Coexisting conditions (%)		
Congestive heart failure	7.1	10.3
Lung disease	9.5	18.0
Cerebrovascular disease	0	18.0
Diabetes mellitus	0	5.1
Renal disease	2.4	12.9
Liver disease	0	2.56
Physical examination		
Temperature (°C)	38.5±1.1	37.5±1.4
Room air saturation (%)	92±4	88±10
Systolic blood pressure	104±13	119±26
Diastolic blood pressure	62±13	66±19
Pulse rate	156±17	107±22
Laboratory results		
Haematocrit (%)	32.9±4.6	39.6±5.7
Sodium (mEq/L)	135.6±4	136±6.8
Creatinine (mg/dL)	0.4±0.2	1.9±1.5
Glucose (mg/dL)	109.7±18.6	133.7±43.7
pH	7.39±0.1	7.33±0.1
PORT score (% of the number of adult group)†		
Class II	NA	12.8
Class III	NA	20.5
Class IV	NA	28.2
Class V	NA	35.9
Length of hospitalisation (days)	6.0±4.6	10. 6±12.6

*Values expressed as mean±SD.

†PORT score was available for 38 adult patients only.

prolonged (11.25±2.25 days in children and 15.5±5 days in adults), as anticipated in complicated pneumonia cases.

In the adult group, three females were in the third trimester of pregnancy (ranging from 35 to 37 weeks). One of them had a normal WBC count on admission while the other two presented with mild and significant leukocytosis, respectively.

Physical examination findings and main blood test results are shown in Table 1. While more than half of the children (57.1%) presented with high fever (>38.5°C), only 20.5% of the adults were febrile at admission. Moreover, five patients (three children and two adults) of the 81 (6.2%) were afebrile and with normal WBC count at presentation. As we have no information on whether or not these patients received antipyretic drugs prior to hospitalisation, this observation is to be taken with circumspection. Room air oxygen saturation <90% was noted in 26.2% of children and in 35.9% of the adult group. No significant statistical difference was found between the clinical and laboratory data of patients presenting with and without leukocytosis.

Table 2 shows the WBC cell count divided into three groups – normal WBC, mild and significant leukocytosis at presentation – in children and adults.

Leukocytosis was marked at presentation in the majority of patients. While 13% (5% children and 8% adults) developed only mild leukocytosis, 51% (30% children and 21% adults) developed significant leukocytosis. The average length of hospital stay in children with mild leukocytosis (n=5) and in those with significant leukocytosis (n=30) was 8.0 and 5.2 days, respectively. In the adult group the average length of hospital stay was longer than in children (9.3 days in the group presenting with mild leukocytosis (n=8) and 10.6 days in patients with significant leukocytosis (n=21)).

Twenty-one percent of all patients (16.7% of children and 25.6% of adults) had a normal WBC count on admission. Most of the adults (90%) presenting with a normal WBC count developed leukocytosis later during their hospitalisation: 50% developed mild leukocytosis and 40% developed significant leukocytosis. Half of the adult patients with mild leukocytosis at presentation developed significant leukocytosis later on during the hospitalisation. The maximal WBC count was observed 5.2±5.1 days after hospitalisation in the adult group.

In the paediatric population, 71% of patients presenting with a normal WBC count developed leukocytosis during their hospitalisation. The highest WBC count appeared within 4.0±1.7 days of hospitalisation.

By multivariate analysis, no variables were found to be associated with the absence of leukocytosis at presentation.

When analysing a subgroup of geriatric patients aged >65 years (15 cases), we found that 20% presented with a normal WBC count and another 20% presented with extreme leukocytosis, compared with 29% and 37.5%, respectively, in the non-geriatric group.

Seven of the 81 patients (8.6%) died during hospitalisation. All the other patients were discharged from hospital in a stable condition.

Serogroup distribution

Eighteen different serotypes were found among 67 patients (36 children and 31 adults), but only five of them accounted for 73.1% of the strains. Serotypes were unavailable for 14

Table 2. White blood cell count at presentation according to age group, length of hospital stay, and outcome

	White blood cell count/mm³			p value
	<10,000	10,000–15,000	>15,000	
No (%) children (n=42)	7 (16.7)	5 (11.9)	30 (71.4)	NS (0.26)
No (%) adults (n=39)	10 (25.6)	8 (20.5)	21 (53.8)	NS (0.26)
Hospital stay, children (days)	8.0±4.6	8.0±5.1	5.2±4.6	NS (0.21)
Hospital stay, adults (days)	11.6±13.9	9.3±12.7	10.6±12.7	NS (0.46)
Adult outcome				
Alive	9	6	17	NS (0.69)
Dead	1 (10%)	2 (25%)	4 (19%)	

NS=non-significant.

patients. The five serotypes found most frequently were 1 (23.9%), 5 (20.9%), 14 (16.4%), 6B (7.4%), and 7F (4.5%). The serotype distribution was similar in both genders. Serotype 14 was ranked first in frequency in children (30.5%) and was exclusive for this population. In the elderly population, serotype 7F was associated with more severe disease at presentation, supported by higher PORT scores. There was no correlation between pneumococcal serotype and WBC count at presentation and/or outcome.

Discussion

CAP is a common disorder which is potentially life-threatening, especially in older adults and patients with co-morbid diseases. Despite all rigorous definitions of pneumonia requiring the finding of a pulmonary infiltrate on a chest radiograph,[5,6,12-14] in daily practice in patients with mild respiratory symptoms and a normal WBC count a chest radiograph will often not be ordered.

In this study we found that 21% of patients with bacteraemic pneumococcal pneumonia presented with a normal WBC count (16.7% of children and 25.6% of adults). These findings are consistent with one previously published study.[8] This detailed analysis of adult bacteraemic pneumococcal pneumonia in a community teaching hospital during the years 1992–1996 found that, among 108 patients, only 73.2% presented with a leukocyte count >11,000 cells/mm³. The authors noted that leukocytosis was associated with a better prognosis than a normal leukocyte count and leukopenia,[8,15] findings that were not confirmed in our study.

Paediatric subgroup

Most children with bacteraemic pneumococcal pneumonia have a typical illness with high temperature, leukocytosis and lobar or segmental consolidation on the chest radiograph.[8,13] However, as many as 30% of patients might have an atypical illness, demonstrating the clinical variability of bacteraemic pneumonia.[7] As shown previously by Toikka *et al*.[7] and confirmed in our study, 17% of children presented with normal WBC on admission. Since our study combined both paediatric and adult populations, we used the definition of leukocytosis (>10,000 cells/mm³) as applicable in the adult population. Although in the paediatric population (mainly aged <6 years) leukocytosis is usually defined as a WBC count ≥15,000 cells/mm³,[7,13] we decided to define leukocytosis according to the adult values so it is possible that even more children would have presented with normal leukocytosis if the adjusted paediatric values had been used.

Geriatric subgroup

In the geriatric population a diagnosis of pneumonia might be challenging since the symptoms and signs of the infection are often incompletely expressed.[16] In our study, analysis of the geriatric subpopulation showed that normal and extreme WBC counts at presentation occurred equally (20% in each group).

An observational study of pneumococcal pneumonia in 70 patients aged ≥80 years showed that pleuritic pain was less frequent in this age group.[17] Nevertheless, in our study 60% of this group presented as classical bacteraemic pneumonia syndrome, defined as the presence of at least three of the following symptoms: acute chest pain, chills, pleuritic chest pain, and purulent sputum.[17] Advanced age is known to be associated with reduced symptoms.[18] Febrile responses to infectious diseases in geriatric patients are often blunted or absent.[19] Leukocytosis and an excess of immature WBC (bandemia) are generally reported less frequently in older patients,[16] although some observational studies point out that the majority of elderly patients with CAP[20] or community-acquired bacteraemic infections tend to develop leukocytosis on presentation.[21] Given the higher frequency of a presentation with non-specific pneumonia in elderly patients, underdiagnosis of this illness can occur, leading potentially to a high rate of complications and death. The mortality rate of CAP doubles as age increases, from 7.8% in those aged 65–69 years to 15.4% in those aged ≥90 years.[22] Our study supports the practice of not focussing on the WBC count in the context of a possible pneumonia.

Serotype analysis

The pneumococcal strain survey showed that serotype 14 was the most common serotype in the paediatric group and exclusive to it. This finding is consistent with data summarised

from 35 studies reported from 16 countries in Western Europe which found that serotype 14 was the most common in a patient population aged <18 years, ranging from 19% to 47%.[23] This strain is included in Prevnar, a heptavalent pneumococcal conjugate vaccine (PCV7) approved by the FDA in February 2003. None of the children in our cohort received the Prevnar vaccine, and this result therefore reinforces the importance of this vaccination in our population.[24] Serotype 7F was restricted to the adult group, being associated with more severe morbidity in the elderly. This serotype is included in the polyvalent pneumococcal vaccine (Pneumovax) which is widely available in most countries. No data were available regarding the Pneumovax immunisation status of the study subjects so we do not know whether the infected cases represented non-immunised patients or cases of vaccine failure.

Guidelines

The need for chest radiography in febrile children is not clear in the literature. One study showed that 25% of young children with a high temperature, WBC count >20,000/mm^3 and no clinical signs of respiratory distress had radiographic signs of pneumonia.[25] In contrast, another study showed that very few infants with fever but no respiratory signs had pneumonia.[26] The British Thoracic Society (BTS)[27] recommends that chest radiography should be considered in young children with pyrexia of unknown origin without reference to the WBC unless features of bronchiolitis are present. The BTS guidelines for the management of CAP in adults (updated in 2009)[28] state that it is not necessary to perform a chest x-ray in patients with suspected CAP unless the diagnosis is in doubt or the progress following treatment for CAP is not satisfactory. However, the guidelines state that all patients admitted to hospital with suspected CAP should have a chest x-ray performed as soon as possible to confirm or refute the diagnosis.

Limitations of the study

Our study closely examines cases of proven pneumococcal pneumonia encompassing a whole range of ages, focusing on the laboratory findings on presentation and over the hospitalisation course. While a retrospective observation allows a precise isolation of the particular disorder, this study design also has a few limitations. First, the sample of the study was relatively small. Second, only hospitalised patients were included, suggesting a bias towards more severe cases. Finally, because we only included patients with positive culture bacteraemia, those with non-bacteraemic pneumococcal pneumonia or non-pneumococcal pneumonia were omitted.

Conclusions

In this study of 81 hospitalised patients with bacteraemic pneumococcal pneumonia, 16.7% of the children and 25.6% of the adults had no leukocytosis at presentation. There was no predictive factor for presenting without leukocytosis. We therefore suggest that every patient with a clinical suspicion of pneumonia should undergo a chest x-ray, even if the WBC count is in the normal range.

Conflicts of interest

None.

Funding

None.

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