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Association of White Blood Cell Count and C-Reactive Protein with Outcomes in Children Hospitalized with Community-Acquired Pneumonia

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INTRODUCTION

Peripheral white blood cell (WBC) count and C-reactive protein (CRP) are obtained frequently among children hospitalized with pneumonia.[1] A number of prior studies indicate poor sensitivity and specificity for differentiating bacterial from viral etiologies for both tests, suggesting little utility for informing antibiotic treatment decisions.[2-9] However, the potential role of WBC count and CRP for predicting disease course and clinical outcomes remains undetermined. Several adult pneumonia studies indicate CRP values may be useful for predicting clinical outcomes,[10, 11] while others suggest little value of such testing.[12] Similar studies have not been conducted in children. Therefore, we sought to determine the association between peripheral WBC count and CRP values with pneumonia outcomes, including fever duration and hospital length of stay (LOS).

METHODS

This study was nested within a multicenter, retrospective cohort of children assembled to validate International Classification of Diseases, 9th revision, Clinical Modification discharge diagnosis codes for community-acquired pneumonia.[13] In that study, we identified 676 children 2 months to <18 years of age hospitalized between January 1, 2010, and December 31, 2010 at 1 of 4 free-standing children's hospitals with provider-confirmed community-acquired pneumonia by medical record review as described previously. The main exposures in this study were CRP (mg/dL) and WBC count ($x10^3$ per mm^3), and only children from the validation study with both tests performed within 24 hours of admission were included (n=153; 22.6%). Outcomes included duration of fever and hospital LOS, both measured in hours. Duration of fever was measured as the time from emergency department arrival until the last recorded temperature >38.0° C (measured per clinical routine, ie, no less than every 8 hours). Additional data collected included patient demographics (age, sex, race/ethnicity, and payor), presence of a complex chronic condition,[14] presence and size (small or moderate/large) of pleural effusion, and admission to intensive care or need for invasive mechanical ventilation within the first 2 calendar days of admission. The institutional review board at each hospital approved the study.

Data were summarized using frequency (%) for categorical variables and median (interquartile range, IQR) values for continuous variables. Associations between the main exposures (WBC count and CRP) and outcomes (duration of fever and hospital LOS) were modeled using multivariable linear regression with an exponential distribution. Models were adjusted for hospital clustering with a random intercept for each hospital. Final models were constructed using backwards elimination that initially included all covariates described above; a priori, the main exposures and age were included regardless of statistical significance. Results are presented as ratios of means with associated 95% confidence intervals. To aid in clinical interpretability of the results, we also modeled the log of length

of stay using a linear mixed effects model clustered on hospital, and back transformed the parameter estimates. All analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC). A 2-sided p-value <.05 was considered significant for all analyses.

RESULTS

The majority of the 153 included children were young (61.4% < 6 years).(See Table, Supplemental Digital Content 1) Twelve children (7.8%) had a complex chronic condition. Nineteen children (12.4%) were admitted to the intensive care unit and 11 (7.2%) required invasive mechanical ventilation within the first two calendar days of admission. The median peripheral WBC count was 14.4×10^3 per mm^3 (IQR: 9.5, 20.1) and the median CRP was 7.5 mg/dL (IQR: 2.5, 19.6). Fever resolved within 24 hours of admission for 103 children (67.3%) and within 48 hours of admission for 117 children (76.5%). None of the included children had fever documented within six hours of discharge. The median hospital LOS was 66 hours (IQR: 44, 134 hours). There were no deaths.

In addition to the main exposures and age (selected a priori), only mechanical ventilation was retained in the final multivariable models, demonstrating a strong association with both hospital length of stay and fever duration (Table 1). Similarly, increasing CRP was associated with increased fever duration (adjusted ratio of means 1.08, 95% CI [1.05, 1.10] and increased length of stay (adjusted ratio of means 1.03, 95% CI [1.00, 1.04]). From the secondary length of stay analysis using multivariable linear regression, we conclude that for every 1mg/dL increase in CRP, length of stay is expected to increase by 1 hour (See Table, Supplemental Digital Content 2). In contrast, neither age nor peripheral WBC count were associated with either outcome.

DISCUSSION

In this multicenter study of children hospitalized with community-acquired pneumonia, C-reactive protein measured within 24 hours of hospital admission was associated with both hospital length of stay and fever duration. Baseline peripheral white blood cell count was not independently associated with either outcome.

Among adults with pneumonia, CRP alone demonstrated good discrimination for predicting hospitalization (area under the curve 0.73),[10] but predicted mortality less well (area under the curve 0.62).[12] The addition of CRP to validated severity scores led to modest improvements in both the ability to predict hospitalization[10] and mortality.[11] Our results indicate that CRP, measured at the time of admission, may also prove useful for predicting outcomes among children hospitalized with pneumonia. As such, CRP should be considered for inclusion in the development of pediatric pneumonia severity scores. Our findings also support the 2011 Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) guidelines for the management of community-acquired pneumonia in children which recommend consideration of acute-phase reactants such as CRP for those with severe disease.[15]

The 2011 PIDS/IDSA guidelines do not recommend routine performance of complete blood counts; instead, the guidelines recommend that complete blood counts be reserved only for

those children with severe pneumonia.[15] For this population, the committee noted the importance of screening for significant anemia or thrombocytopenia, which may herald more serious complications. In contrast, the committee emphasized the lack of predictive ability of WBC count for distinguishing bacterial from viral etiologies. While our study did not examine etiology, our findings further highlight the poor utility of WBC count by failing to demonstrate an association between WBC count and disease outcomes. Thus, while complete blood counts may help identify complications in those with severe pneumonia, reliance on the WBC count to help guide management decisions should be discouraged.

Our study has several limitations, largely related to the retrospective observational design. Only a fraction of children in the larger validation study with provider-confirmed pneumonia had both CRP and WBC count measured during the first 24 hours of admission (see Table, supplemental digital content 1). It is likely that our study represents a more severe population and may not be directly generalizable to a non-selective population of children hospitalized with pneumonia. Although a number of covariates were considered for inclusion in the multivariable models, there is potential for residual confounding due to unmeasured factors. Finally, while low WBC count may also portend worse outcomes, the paucity of children with leukopenia in this cohort (n=6) precluded meaningful sub-analysis. Given these limitations, it will be important to confirm our findings in future prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association of C-reactive Protein and Peripheral White Blood Cell Count with Length of Stay and Duration of Fever for Children Hospitalized with Pneumonia

	Hospital Length of Stay		Duration of Fever	
Variable	**Adjusted Ratio of Means (95% CI)**	**P-Value**	**Adjusted Ratio of Means (95% CI)**	**P-Value**
Age				
0-5 years	1.17 (0.82, 1.64)	0.378	0.92 (0.63, 1.34)	0.668
≥6 years	Reference		Reference	
Mechanical ventilation	4.37 (2.34, 8.17)	<.001	2.83 (1.48, 5.39)	0.002
White blood cell count	1.01 (0.98, 1.03)	0.628	0.99 (0.96, 1.01)	0.307
C-reactive protein [a]	1.03 (1.00, 1.04)	0.007	1.08 (1.05, 1.10)	<.001

Adjusted ratio of means estimated using multivariable linear regression with an exponential distribution; all variables included in the model are listed in the table;

[a] For every 1mg/dl increase in C-reactive protein, hospital length of stay increases by 3% and duration of fever increases by 8%.