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MAJOR ARTICLE

White Blood Cell Counts, Alcoholism, and Cirrhosis in Pneumococcal Pneumonia

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Background. An elevated white blood cell (WBC) count is a characteristic finding in pneumococcal pneumonia. Very low WBC counts, occurring in some cases, are often associated with overwhelming pneumonia and have been attributed to alcohol-induced suppression of bone marrow. However, a systematic study of neutropenia, leukocytosis, alcohol ingestion, and cirrhosis in pneumococcal pneumonia has not been previously reported.

Methods. Using a database of patients with pneumococcal pneumonia at our medical center, we extracted data on WBC counts at admission, differential counts, alcohol ingestion, and cirrhosis, and we related these to 7-day and 30-day mortality.

Results. White blood cell counts were <6000/mm^3 in 49 of 481 patients (10.2%) with pneumococcal pneumonia and >25 000/mm^3 in 40 (8.3%). Mortality at 7 days was 18.4% and 12.5%, respectively, 5-fold and 3-fold greater in patients with WBC <6000 or >25 000 than in those with WBC counts between 6000 and 25 000 ($P < .001$). Increased band forms were not associated with a worse outcome ($P = .12$). Alcohol use and cirrhosis were not associated with WBC counts <6000 ($P = .63$ and $P = .41$, respectively).

Conclusions. In a large series of cases of pneumococcal pneumonia, WBC counts <6000 or >25 000 correlated significantly with increased 7-day mortality. More than 10% band forms was not associated with a poor outcome. Alcohol abuse was not associated with low WBC or increased mortality. Our findings suggest that greater consideration be given to more intense care for patients with bacterial pneumonia who have very high or very low WBC counts at the time of hospital admission.

Keywords. alcoholism; leukocytosis; neutropenia; pneumonia; white blood cell count.

The white blood cell (WBC) count is generally expected to rise in response to infection and has long been used by clinicians to help diagnose pneumonia, determine its etiology, and predict patient outcomes [1, 2]. However, up to 25% of patients hospitalized for pneumococcal pneumonia [3] and up to 38% hospitalized for community-acquired pneumonia (CAP) [4] have a normal WBC count at the time of admission. Relatively few studies have examined in depth the relationship between WBC counts and prognosis. A low WBC count has often been said to be associated with poor outcomes both in bacteremic and nonbacteremic pneumococcal pneumonia, but not all studies have come to the same conclusion (Table 1). There is even less consensus about the prognostic value of very high WBC counts in pneumococcal pneumonia. Alcoholism has always been common among patients with pneumococcal pneumonia [2], and some investigators say that it increases mortality in pneumococcal [5, 6] or CAP [7, 8], but others have said that it has no effect on disease outcome [9, 10] (Table 1). Neutropenia in pneumonia is often attributed to the effect of alcohol ingestion [5, 11, 12].

To our knowledge, no previous study has systematically evaluated the prognostic significance of neutropenia, leukocytosis, and increased early forms (bandemia) in a single cohort of patients with pneumococcal pneumonia or has reported on the association of these factors with alcohol ingestion. We now present the results of such a study.

METHODS

Study Design

Using a database of all patients with pneumococcal infection seen at the Michael E. DeBakey Houston VA Medical Center since 2000, we selected those who were hospitalized from 2000 to 2013 with a final diagnosis of pneumococcal pneumonia. In accordance with the Centers for Disease Control and Prevention definitions, cases were stratified into the following: (1) proven pneumococcal pneumonia, a clinical syndrome of pneumonia with isolation of *Streptococcus pneumoniae* from the blood or another normally sterile body site; and (2) presumptive pneumococcal pneumonia, a clinical syndrome of pneumonia with a consistent sputum Gram stain and a sputum culture yielding *S*

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Table 1. Previous Reports of Prognostic Value of WBC Counts in Patients With Pneumococcal or Community-Acquired Pneumonia

Author	Only *Streptococcus pneumoniae*	↓ WBC as Risk[a]	Definition (WBC/mm^3)	Statistical Analysis	Odds Ratio or *P* Value	↑ WBC as Risk	Definition	Statistical Analysis	Alcohol Use as Risk	Statistical Analysis	Odds Ratio or *P* Value
Heffron [2]	Yes	Yes	<10 000	No	ND	Yes	>40 000	No	NR	—	—
Austrian and Gold [9]	Yes	Yes Yes	<5000 5–9000	No No	ND ND	Yes	>25 000	No	No	No	ND
Chomet and Gach [5]	No	Yes	<6000	No	ND	No	—	—	Yes	No	ND
Hook et al [10]	Yes	Yes	<5000	Yes	*P* < .001	NR	—	—	NR	—	—
Perlino and Rimland [12]	Yes	Yes	≤4000	Yes	*P* < .001	NR	—	—	No	Yes	*P* > .05
Chang and Mylotte [23]	Yes	No	<5000	Yes	*P* > .05	No	>25 000	Yes	NR	—	—
Ortqvist [6]	Yes	Yes	<9000	Yes	*P* < .05	NR	—	—	Yes	Yes	*P* < .01
Leroy et al [24]	No	Yes	<3500	Yes	OR 5.0	NR	—	—	NR	—	—
Watanakunakorn and Bailey [25]	Yes	Yes	<3000 3–11 000	Yes Yes	*P* < .001 *P* < .001	NR	—	—	NR	—	—
Mortensen et al [7]	Yes	Yes	<4000	Yes	OR 2.99	NR	—	—	Yes	Yes	*P* < .01
Martens et al [26]	Yes	Yes	<9000	Yes	OR 2.76	NR	—	—	No	Yes	*P* > .05
Menendez et al [27]	No	Yes	<4000	Yes	OR 3.7	NR	—	—	NR	—	—
Paganin et al [8]	No	Yes	<1000	Yes	OR 2.48	NR	—	—	Yes	Yes	RR 3.11
Marrie and Wu [28]	No	Yes	<1000[b]	Yes	OR 2.05	NR	—	—	NR	—	—
Furer et al [3]	Yes	No	<10 000	Yes	*P* = .69	No	>25 000	No	NR	—	—
Blot et al [16]	Yes	Yes	<4000	Yes	OR 13.7[c]	NR	—	—	No	Yes	*P* > .05

Abbreviations: ND, not done; NR, not reported; OR, odds ratio; RR, relative risk; WBC, white blood cells.

[a]Risk in every study referred to death, except Menendez et al [27], which referred to treatment failure.

[b]Table 4 in this reference lists lymphocytes, which we believe is in error.

[c]Statistical analysis of a leukocyte score (neutropenia, lymphopenia, and monocytopenia).

pneumoniae as the predominant isolate, but without blood culture confirmation.

Electronic medical records were reviewed, and the initial WBC count and differential at the time of presentation were extracted. We determined mortality 7 and 30 days after admission. Patients with leukemia or medication-induced neutropenia were excluded, but we did not exclude patients with cirrhosis, human immunodeficiency virus infection, or other immunocompromising conditions. Alcohol abuse was defined as either a diagnosis of alcoholism or alcohol abuse or the documentation in the medical record of regular consumption of >6 drinks per day at any time during the preceding 2 years. We also included in this category patients who had previously been diagnosed alcohol abusers if the medical record stated more vaguely that, for example, they were now "drinking again." Cirrhosis was diagnosed based on review of all discharge summaries.

Statistics

Descriptive data were reported as mean ± standard deviation for continuous variables and as frequencies and proportions for categorical variables. Differences across groups were compared using the χ^2 test for categorical variables and the unpaired *t* tests or Kruskal-Wallis test for continuous variables as appropriate. Survival at 7 days and 30 days of different groups of WBC were

Table 2. Factors Associated With Increased 7- or 30-Day Mortality in Patients With Pneumococcal Pneumonia

Variable	No. of Patients	Mortality		Hazard Ratio	*P* Value[a]
		7-Day	30-Day		
WBC <6000	49	18.4%	30.6%	5.66	<.001
WBC 6000–10 000	85	5.9%	8.2%	1.49	.50
WBC 10 000–25 000	307	3.3%	11.1%	(Reference)	
WBC >25 000	40	12.5%	12.5%	3.94	.01
Immature forms ≤10%	412	5.3%	12.4%	(Reference)	
Immature forms >10%	69	10.1%	14.5%	3.59	.23
Bacteremia	164	9.8%	15.2%	2.08	.06
Alcohol abuse	105	8.6%	13.3%	1.80	.22
Cirrhosis	27	14.8%	18.5%	3.11	.048

Abbreviations: WBC, white blood cells.

[a]Compared to patients with 10 000–25 000 WBC.

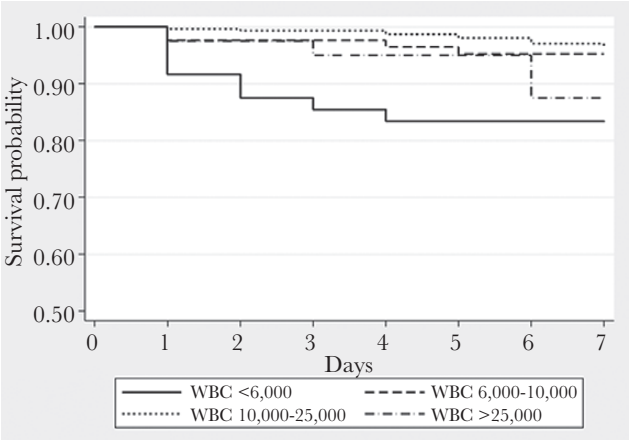

Figure 1. Kaplan-Meier curve for 7-day survival. WBC, white blood cells.

depicted using Kaplan-Meier methodology. Univariate and multivariate Cox proportional-hazards models were used to determine the contribution of potential risk factors to risk of death. Results were reported as hazard ratios and 95% confidence intervals. All analyses were performed on Stata, version 13.1 (StataCorp LP, College Station, TX). A *P* value of <.05 was considered statistically significant.

RESULTS

Our database listed 481 patients with pneumococcal pneumonia. Of these, 49 (10.2%) had WBC counts <6000, 85 (17.7%) had 6000–9999 WBC, 307 (63.8%) had WBC 10 000–24 999, and 40 (8.3%) had WBC >25 000 (Table 2). Overall mortality at 7 days was 6.0%: 18.4% in patients with WBC <6000, and 12.5% in those with WBC >25 000, significantly greater than the mortality of 3.8% in those with WBC counts of 6000 to 25 000 ($P < .001$) (Table 2, Figure 1). At 30 days, mortality remained higher in patients who had been leukopenic at admission, but the difference was no longer significant for those who had had leukocytosis (Table 2).

A high number of early WBC forms was not associated with mortality. Thirty-four patients (7.1%) had 5%–10% bands, and 69 (14.3%) had >10% bands. There was no association between elevated band counts and mortality ($P = .12$). In fact, patients with >30% band forms appeared to have a lower mortality than those with 10%–20%, although small numbers of subjects precluded statistical analysis (Table 3). Alcohol abuse was cited in the records of 12 of 49 (24.5%) patients with WBC counts <6000 vs 93 of 432 (21.5%) in all patients with WBC ≥6000 ($P = .63$). Of 49 patients with WBC counts <6000, 4 (8.2%) had documented cirrhosis, vs 23 of 432 (5.3%) with WBC ≥6000 ($P = .41$). We found a tendency toward increased mortality among alcohol abusers, but even in our large series of cases, this number did not reach statistical significance (odds ratio [OR] = 1.80, $P = .22$) (Table 2). The rate of death in patients with cirrhosis was significantly greater than in those without cirrhosis (14%; OR = 3.11, $P < .05$).

Table 3. Mortality and Presence of Band Forms

		Mortality	
Band Forms (%)	Number of Patients	7 Days	30 Days
0–10	412	5.3%	12.4%
11–20	41	17.1%	19.5%
21–30	14	0%	7.1%
31–40	7	0%	0%
>40	7	0%	14.3%

To relate WBC counts to bacteremia, we excluded 35 patients whose blood was not cultured and 18 who had received antibiotics before blood cultures were obtained. In the remaining 428 cases, 23 of 41 with WBC <6000 (56.1%) were bacteremic, significantly higher than the 36.0% of patients with WBC 6000–25 000 ($P = .01$) (Table 4). The incidence of bacteremia in patients with WBC >25 000 (15 of 37; 40.5%) was not greater than in those with WBC between 6000 and 25 000 ($P = .59$). At day 7 of hospitalization, mortality was greater among bacteremic than nonbacteremic patients (16 of 164 [9.8%] vs 12 of 264 [4.5%]; $P = .03$), but this difference was not significant at 30 days (mortality = 15.2% and 12.5%, respectively; $P = .42$). Mean WBC counts in bacteremic and nonbacteremic cases were similar (15 100 per mm^3 ± 790 vs 14 500 ± 690, respectively; $P = .45$).

DISCUSSION

The results of the present study show that patients with pneumococcal pneumonia who, at the time of presentation, have WBC counts <6000 per mm^3 have a >5-fold increase in the risk of death at 7 days compared with patients whose WBC counts are between 10 000 and 25 000. In the same comparison,

Table 4. Bacteremia and WBC Counts

WBC Count	Number (%, 481 Total)	Number With Culture (%, 428 Total)	Bacteremia (%, 164 Total)	*P* Value[a]
<6000	49 (10.2%)	41 (9.6%)	23 (56.1%)	.012
6000–10 000	85 (17.7%)	73 (17.1%)	20 (27.4%)	—
10 000–25 000	307 (63.8%)	277 (64.7%)	106 (38.3%)	—
>25 000	40 (8.3%)	37 (8.6%)	15 (40.5%)	.585

Abbreviations: WBC, white blood cells.

[a]Compared with patients with 10 000–25 000 WBC.

patients with WBC counts >25 000 had a >3-fold increase in mortality at 7 days. Somewhat surprisingly, we found no association between elevated band forms and outcome, and, paradoxically, the 7-day mortality actually appeared to decrease with >20% bands, although the sample size was very small (see Table 3). The high mortality in the 10%–20% group could indicate inadequate production of immature forms in some patients with bandemia in response to severe infection. Bacteremia was associated with increased mortality at 7 days but not at 30 days, probably because acuity of the disease caused death initially, whereas complications of the pneumonia were responsible for death at 30 days; others who have reported a lack of association between bacteremia and outcome [13] have focused on 30-day mortality.

Most but not all previous studies have shown that low WBC counts are associated with a poor outcome in patients who have pneumococcal pneumonia (Table 1). An association between extremes of WBC counts and death from pneumococcal pneumonia was noted as long ago as 1917 [14]. However, only a very few studies have provided data together with statistical analysis, and, to our knowledge, no previous study has analyzed the associations among low or very elevated WBC counts and mortality in a single cohort of patients. Some earlier investigators stated that alcohol ingestion is associated with a worse outcome in pneumococcal pneumonia [5, 6, 15], whereas others [9, 10] did not agree. Multivariate statistical analysis was not done in these studies but, in our study, revealed no significant association between mortality and alcohol ingestion. Cirrhosis was associated with >3-fold risk for mortality.

Based on anecdotal reports, earlier investigators attributed low WBC counts in pneumococcal pneumonia to toxic suppression of the bone marrow by alcohol [5, 11]. Perlino and Rimland [12] reported a significant association between alcoholism and WBC ≤4 000 per mm^3 in pneumococcal pneumonia. However, the present study with a much larger group of patients failed to confirm this finding: neither alcohol use nor cirrhosis was associated with WBC counts <6000 ($P = .63$ and $P = .41$, respectively). Blot et al [16] developed a leukocyte score based on neutrophil, lymphocyte, and monocyte counts, and they found no association between alcoholism and this leukocyte score, consistent with our findings. In more recent years, suppression of hematopoiesis by cytokines and exhaustion of marrow reserves have been cited as the causes for low WBC counts in sepsis [17], but the presence of large numbers of early forms (bands and metamyelocytes) in the peripheral blood appears to oppose this hypothesis.

Instead, we propose the following hypothesis to explain neutropenia in serious bacterial infections: acute bacterial infection stimulates the release of cytokines, such as tumor necrosis factor-α, interleukins 6 and 8, granulocyte-colony stimulating factor, and CXCL-12, that mobilize the release of mature PMNs and immature forms (bands and metamyelocytes) from bone marrow [18, 19]. Infection also stimulates release of soluble E-selectin [19], triggering the complement cascade and activating vascular endothelium, especially in the lungs, causing intravascular leukostasis and capillary plugging by mature polymorphonuclear leukocytes [20–22]. As a result of these factors, the number of immature forms increases, while the number of circulating mature neutrophils declines. The final outcome depends upon the balance among these factors and the host's response to them. Some patients with pneumococcal pneumonia who go untreated may initially have elevated WBC counts that then fall as the infection progresses, presumably depending upon the balance among the cytokines that are produced (D. M. M., unpublished observations, 1973–2015 and reference [5]).

CONCLUSIONS

In summary, in this study of a large number of patients with pneumococcal pneumonia, WBC counts that were very low (<6000) or elevated (>25 000) correlated significantly with bacteremia and increased mortality. Bandemia was not associated with death. Neither alcoholism nor cirrhosis appeared to be responsible for the neutropenia. These data suggest that more intense care be regularly given to patients with pneumococcal pneumonia, and perhaps any bacterial pneumonia, who have very high or very low WBC counts.

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