

Age-Related Leukocyte and Cytokine Patterns in Community-Acquired Bronchopneumonia

Ami Ballin MD^{1,3}, Alla Osdachi MD², Amir Klivitsky MD¹, Ilan Dalal MD^{1,3} and Michael Lishner MD^{2,3}

¹Department of Pediatrics, Wolfson Medical Center, Holon, Israel

²Department of Internal Medicine A, Meir Medical Center, Kfar Saba, Israel

³Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Abstract

Background: Community-acquired bronchopneumonia in children is frequently accompanied by extreme leukocytosis, whereas in adults with the same diagnosis a high leukocyte count is uncommon. Data regarding differences in the serum levels of inflammatory cytokines between children and adults are limited.

Objectives: To compare leukocyte counts and blood levels of various inflammatory cytokines in children and adults diagnosed with community-acquired bronchopneumonia.

Methods: We prospectively evaluated all pediatric and adult patients admitted for bronchopneumonia based on clinical and chest X-ray findings. Blood was drawn for complete blood count and serum concentration of the following cytokines: granulocyte colony-stimulating factor, interleukins-6, 8 and 10, interferon-gamma, tumor necrosis factor, as well as matrix metalloproteinase-9 and intercellular adhesion molecule-1.

Results: There were 31 children and 32 adults. The patients in both groups had similar parameters of infection severity. None of them required admission to the Intensive Care Unit. Mean (\pm SD) leukocyte counts in the pediatric and adult groups were 21,018/mm³ (\pm 10,420) and 12,628/mm³ (\pm 6735) respectively ($P = 0.02$). Age was inversely correlated with leukocytes in the pediatric group ($P = 0.0001$). A significant inverse correlation was also found between age and platelet counts. Although cytokine levels in both groups were not significantly different, age was directly correlated with MMP-9 ($P = 0.03$), IL-8 ($P = 0.03$) and G-CSF ($P = 0.014$).

Conclusions: The immune response in community-acquired bronchopneumonia is, at least partly, age-dependent.

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We have observed that community-acquired bronchopneumonia in children is frequently accompanied by extreme leukocytosis, while in adults with the same diagnosis a high leukocyte count is uncommon. The role of endogenous granulocyte colony-stimulating factor in maturation and function of neutrophils is well documented [1,2]. Less is known about age-related G-CSF levels. Similarly, much has been written about the involvement of various cytokines in the pathogenesis of pneumonia [3-8], but only limited data are available regarding differences in the serum levels of these cytokines between children and adults. Some of the cytokines associated with pneumonia in adults are intercorrelated [9]. Such a correlation – as well as a possible association

between leukocyte numbers and the involved cytokines – has not been well characterized in the various age groups. Our observation led us to investigate the leukocyte response and cytokine pattern in children and adults suffering from bronchopneumonia.

Patients and Methods

The study was carried out in the Pediatric Department at the Wolfson Medical Center and the Department of Internal Medicine A at Meir Medical Center. The study was approved by the institutional ethics committees. Included were all patients admitted to the hospitals from May 2002 to December 2003 due to bronchopneumonia diagnosed by the following criteria: symptoms of fever $> 38.5^{\circ}\text{C}$ and cough, signs in the physical examination, and compatible X-ray findings. Excluded were patients known to have chronic diseases including asthma or hyper-reactive airways disease, and patients on antibiotics, steroid therapy or any drug that may affect blood counts.

On admission, blood was drawn for complete blood count. This was quantitated by automated Coulter Counter (Coulter Co., USA). In addition, blood was obtained, separated and frozen at -20°C until analysis of various cytokines, including interleukins-6, 8 and 10, interferon-gamma, matrix metalloproteinase, G-CSF, and soluble intercellular adhesion molecule-1. Cytokine quantitation was performed using enzyme-linked immunosorbent assay kits (Research and Diagnostics Co., USA). The severity of the pneumonia was assessed by the following parameters: respiration rate, oxygen saturation (measured by pulse oximeter, Novametrics Medical Systems, USA) in the first 24 hours of hospitalization, number of pulmonary lobes involved (according to X-rays), and length of hospitalization.

Statistical analysis

Means and standard deviations were determined for all parameters. Spearman's test and the Mann-Whitney test were used for correlations and comparison of means, respectively.

Results

There were 32 children (18 males) and 31 adults (19 males). The mean (\pm SD) age in the pediatric and adult groups was 4.8 years (\pm 4.2) and 42.5 years (\pm 16.4) respectively. The children and adults had similar parameters of infection severity, including respiration rate (relative to normal respiration rates that are different among

IL = interleukin

G-CSF = granulocyte colony-stimulating factor

MMP = matrix metalloproteinase

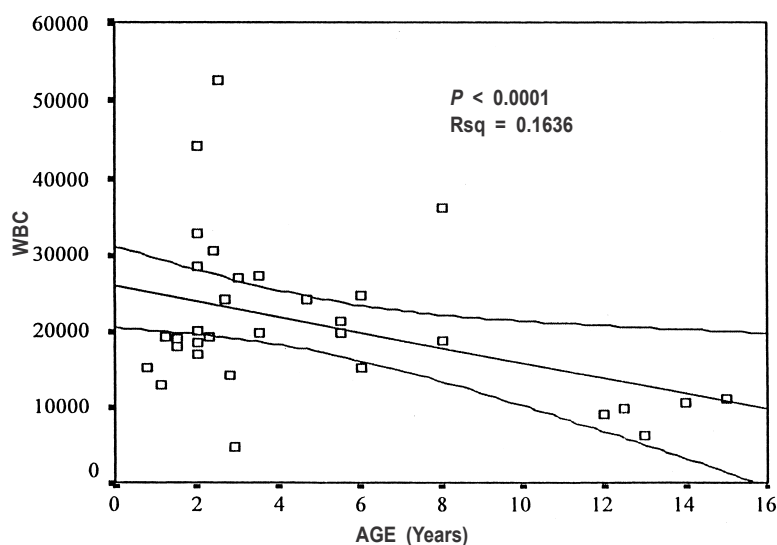


Figure 1. Leukocyte counts and age in children diagnosed with bronchopneumonia.

infants, children and adults), oxygen saturation, number of pulmonary lobes involved, and length of stay (data not shown). No patient required mechanical ventilation or was in septic shock.

Arterial blood gases were not tested in every patient. Mean (\pm SD) leukocyte counts in the pediatric and adult groups were: 21,018/mm³ (\pm 10,420) and 12,628/mm³ (\pm 6,735) respectively ($P = 0.02$). Mean (\pm SD) percentage of neutrophils in the pediatric and adult groups were: 88% (\pm 7) and 72% (\pm 15) (not significant). Mean (\pm SD) of hemoglobin levels in the pediatric and adult groups were: 11.87 g/dl (\pm 0.49) and 12.37 g/dl (\pm 1.54) respectively (NS). Mean (\pm SD) of platelet counts in the pediatric and adult groups were 247,784/mm³ (\pm 106,542) and 233,674/mm³ (\pm 112,435) respectively (NS).

None of the cytokine variables differed significantly between the pediatric and adult groups. However, there were significant differences within each group separately. The following are the results in the pediatric group: Age was inversely correlated with leukocytes ($P = 0.0001$) [Figure 1]. A significant inverse correlation was found also between age and platelet counts. White blood cells were inversely correlated with G-CSF ($P = 0.014$). Age was directly correlated with MMP-9 ($P = 0.03$), IL-8 ($P = 0.03$) and G-CSF ($P = 0.014$). IL-8 was directly correlated with IL-6 ($P = 0.02$) and G-CSF ($P = 0.008$). In the adult group, a significant correlation was found between WBC and IL-6 ($P = 0.009$), WBC and interferon ($P = 0.032$), IL-10 and MMP-9 ($P = 0.04$). In the entire study population we found a significant inverse correlation between WBC and MMP-9 ($P = 0.04$). A significant correlation was found between IL-10 and IL-6 ($P = 0.02$).

Discussion

In this prospective study on pediatric and adult patients diagnosed with community-acquired bronchopneumonia, a signifi-

cantly higher WBC count was found in the pediatric group. From the clinical point of view it should be mentioned that the severity of the pneumonia was similar in both age groups. None of the patients suffered from bilateral infection or septic shock, and no patient was transferred to the Intensive Care Unit.

The inverse correlation between age and WBC in the pediatric group is shown in Figure 1. The younger the patient the higher the leukocyte response. Slight differences in leukocyte counts between children and adults exist in normal healthy individuals [10]. However, these differences exist between adults and children to the age of 6 years only, and are not so extreme as evident in our study of leukocytosis in community-acquired bronchopneumonia. Lin and Huang [11] reported that leukocytosis and thrombocytosis occurred more frequently in children during acute attacks of Henoch-Schönlein purpura than in adults. Ayomama and colleagues [12] compared pertussis in children and in adults. The latter showed neither leukocytosis nor lymphocytosis. Similar differences are

found in response to snakebite. Leukocytosis was documented in 54% of affected children compared to 13% of adults [13].

The more enhanced myeloid reaction of the pediatric group to bronchopneumonia can be explained by the different presumptive pathogens. Since we did not identify the pathogens involved in our patients, we cannot comment on their specific effects. Obviously, pathogens may have an impact on the cytokine profile. It may be speculated that pneumococci are the main pathogens in pediatric patients while Mycoplasma or viruses are responsible for the pneumonia in adults. Barklett and Mundy [14] report on the pathogens of acquired pneumonia in adults based on published reports from North America and from the British Thoracic Society. In opposition to the above-mentioned speculation, bacterial infections account for the great majority of pneumonia in adults while viruses are the pathogens in only 5–15% of cases.

Moreover, even within the age group of pneumococcal infections (3 months to 3 years) we found a decline in leukocyte counts with advanced age. Another explanation for the exaggerated response of the children is age-dependent myelopoiesis. Kumagai et al. [15] examined the response of mice to lipopolysaccharide administration. The response of old mice after administration of lipopolysaccharide differed from that of young mice in diminished proliferative pool of femoral colony-forming units-granulocyte macrophages and splenic CFU-GMs. Similar results, in humans, were reported by Marley and co-workers [16]. They demonstrated that the proliferative capacity of CFU-GM in normal blood and marrow decreases exponentially with age. Looney et al. [17] found that older subjects produced significantly fewer INF γ in response to respiratory syncytial virus than young subjects. Age-related changes occur also in absolute numbers

CFU-GMs = colony-forming units-granulocyte macrophages

INF γ = interferon-gamma

and percentage of lymphocyte subsets [18,19]. Like leukocytes in our study, platelet counts were also inversely correlated with age in the pediatric group.

The clinical picture of an inflammatory process (like pneumonia) is the sum of leukocyte functions and the effect of various cytokines. A significant correlation was found in our study between WBC and serum levels of various inflammatory cytokines. In the pediatric group IL-6 and IL-8 were intercorrelated, as were IL-10 and MMP-9 in the adults and IL-10 and IL-6 in the entire group. Such a correlation is well documented in other studies. Tanaka et al. [3] showed that circulating IL-18 had a positive correlation with serum interleukin-2 receptor levels in adult patients suffering from *Mycoplasma pneumoniae* pneumonia. Che and collaborators [9] found a positive relationship between serum tumor necrosis factor- α and IL-8 in children with low respiratory tract infection caused by this pathogen. Similar direct correlation exists between IFN α , TNF α and IL-1 and bronchoalveolar inflammation cell numbers in pigs inoculated with influenza virus [6]. Hozumi A and co-workers [7] have shown that TNF α induces the expression of MMP-9 in human bronchial epithelial cells.

There was a significant correlation in our pediatric group between age and some cytokines, namely IL-8 and G-CSF as well as MMP-9. Bruunsgaard and Pedersen [20] claim that systemic levels of TNF α increase with age. The direct correlation of age and G-CSF along with the inverse correlation of age and WBC may be explained by high sensitivity of the marrow in the young to G-CSF, a sensitivity that declines with age. The finding by Gessler et al. [21] that the percentage of neutrophils expressing G-CSF receptors is lower in newborns than in adults supports this assumption.

The timing of blood sampling for cytokine serum levels is important. Wang and collaborators [22] have shown that TNF α concentrations in patients with bacterial pneumonia in acute stage were significantly higher than those in convalescent stage. In both hospitals we examined the situation on admission.

In summary, we have shown that leukocyte and some inflammatory cytokine responses to community-acquired bronchopneumonia are, at least partly, age-dependent. Further studies on these and other cytokines are warranted to clarify the role of each factor and the relationship among them in the pathogenesis of pneumonia in children and adults.

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Correspondence: Dr. A. Ballin, Head, Dept. of Pediatrics, Wolfson Medical Center, P.O. Box 5, Holon 58100, Israel.

Phone: (972-3) 502-8421

Fax: (972-3) 502-8164

email: ballin@wolfson.health.gov.il