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Original Article

Evaluation of Eosinophilia in Hospitalized Preterm Infants

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OBJECTIVE:

To characterize changes in eosinophil counts over time, and to draw comparisons across four gestational age groups with respect to the incidence of, and clinical conditions associated with eosinophilia over the first months of life in a single neonatal intensive care unit (NICU).

STUDY DESIGN:

Weekly complete blood counts (CBCs) were collected from all NICU patients. Eosinophilia was classified as mild, moderate, or severe. Changes in eosinophil counts were examined over time, the incidence of eosinophilia was determined by gestational age group, and clinical correlations sought.

RESULTS:

Eosinophil data from 1652 CBCs were analyzed from 332 infants. Eosinophilia occurred in 148 infants (45%) during their hospitalization. The prevalence, severity, and timing of eosinophilia varied by gestational age, infection, and red blood cell transfusions.

CONCLUSIONS:

The incidence and severity of eosinophilia increased with immaturity, and was temporally associated with infection, necrotizing enterocolitis, and packed red blood cell transfusion.

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INTRODUCTION

Eosinophils are granulocytes that dwell for the most part in tissues, and commonly localize to the gastrointestinal mucosa.[1] Eosinophil production in bone marrow is primarily regulated by three cytokines: interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[2] Eosinophils circulate for an estimated half-life of 18 hours prior to entering tissues in response to chemotactic factors such as leukotriene B4, platelet activating factor, interleukins, and eotaxin-1. The granules secreted by eosinophils contain proinflammatory cytokines, chemokines, growth factors, and four cytotoxic molecules specific to eosinophils: eosinophil peroxidase, major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin.[3–6] Eosinophil functions include phagocytosis of antigen–antibody complexes, destruction of parasites, and immune modulation.[1] They are frequently involved in allergic responses. Eosinophilia is defined in neonates as an eosinophil count $\geq$700 cells/mm^3, and has been further subclassified as mild (700 to 999 cells/mm^3), moderate (1000 to 2999 cells/mm^3), or severe (>3000 cells/mm^3).[7–9]

Eosinophilia is common in hospitalized preterm and term newborns, with the reported incidence ranging from 14 to 76%.[7,9,10] As the role of eosinophils in newborns is not well understood, the clinical significance of eosinophilia in neonates is unclear. Many hypotheses have been proposed to explain the cause of eosinophilia in neonates. In 1950 Medoff and Barbero[11] suggested that the rise and fall of circulating eosinophils reflected birth-related stress and corresponding changes in cortisol levels. Other conditions thought to be associated with eosinophilia included the achievement of an anabolic state,[7] antigen exposure due to disease, or invasive procedures including intravenous lines and endotracheal intubation.[8] Eosinophilia has also been associated with infection (bacterial, viral, fungal),[9,12,13] antibiotic use,[14] transfusion of blood products,[10] eosinophilic leukemia,[15] hypereosinophilic syndrome,[16–19] thrombocytopenia with absent radius,[20] chronic lung disease,[21] and exposure to antigens in parenteral nutrition.[10] In addition, there is some evidence that elevated eosinophil counts can be a marker of atopy in newborns, with predictive value for identifying infants with a high risk for developing atopic disease during the first 18 months of life.[22,23]

Over the last 15 years, survival of infants 23 to 26 weeks of gestation has improved significantly. We have recently identified an increased risk of neutropenia and anemia in these extremely preterm infants as compared to more mature infants.[24,25] Eosinophil counts have not been thoroughly evaluated in this group of infants. Therefore, we retrospectively evaluated the eosinophil counts from 332 infants ranging from 23 weeks gestation to term. We hypothesized that the most immature infants (<27 weeks gestation) would be at greater risk for eosinophilia. We report differences in the time course, incidence, and severity of eosinophilia in neonates born at different gestational ages, and the

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corresponding associations between clinical conditions and eosinophilia.

METHODS

All infants admitted to the University of Washington Neonatal Intensive Care Unit (UW-NICU) between February 1, 2001 and March 31, 2002 were eligible for this study. As part of routine clinical care, each infant had a weekly complete blood count (CBC) with differential count performed. Data from additional CBCs were recorded when available. Infant gestational age, birth weight, Apgar scores, drug exposure, transfusions, and clinical diagnoses were documented, as well as maternal diagnoses and maternal drug exposure at time of delivery. Medical records were reviewed retrospectively. Infants with chromosomal anomalies or incomplete data (no eosinophil counts available) were excluded. The most precise gestational age (determined respectively in order of preference: first trimester ultrasound or in vitro fertilization, later prenatal ultrasound, last menstrual period, or estimation by a neonatologist), was used to divide data into groups according to weeks of gestation completed at birth as follows: less than 27 weeks, 27 to 29-6/7 weeks, 30 to 34-6/7 weeks, and 35 weeks or older. The Institutional Review Board of the University of Washington approved the use of these data.

Blood samples were obtained in EDTA tubes, and white blood cell counts were measured by flow cytometric analysis at the UW Department of Laboratory Medicine using the Abbott CellDyn 3500 (Chicago, IL). The automated counters undergo quality control accuracy checking three times per day using calibrated standards. For all differential CBCs ordered for neonates, a technician manually scans the corresponding slides to confirm the automated assessment. Eosinophilia was defined as an absolute eosinophil count ≥ 700 eosinophils/mm^3. This condition was further categorized as mild (700 to 999 cells/mm^3), moderate (1000 to 2999 cells/mm^3), or severe (>3000 cells/mm^3).[7–9]

Infants were first categorized according to gestational age at birth. Documented infection (culture-proven sepsis, or meningitis), presumed infection (symptomatic infant with negative culture results, yet treated with a full 7 to 10-day course of antibiotics), and necrotizing enterocolitis (NEC) were documented. Infants exposed to pregnancy-induced hypertension (PIH) or diagnosed as small for gestational age (SGA)[26] were initially evaluated separately because these conditions can affect hematologic indices such as platelet and neutrophil counts. In the final analysis, PIH and SGA were categorized together because these conditions were 95% coincident. Five infants were SGA due to placental insufficiency in the absence of PIH. To evaluate time course data, all available eosinophil counts from each individual were averaged to produce a single value for each week. Weekly values then underwent nonparametric repeated measures analysis by generalized means estimation (Stata, College Station, TX), followed by Tukey's or Dunnett's post hoc comparisons (SPSS, Chicago, IL). Effects of age on incidence rates were evaluated by χ^2 analysis. Mann-Whitney *U*-test was used to evaluate effects of infections. Results of generalized means estimation are reported as mean $\pm$ SEM; $p<0.05$ was considered significant. Eosinophil counts taken proximal to infection (within 7 days plus or minus) were considered to be influenced by infection. A possible association between eosinophilia and packed red blood cells (PRBC) transfusion was evaluated during the 7-day period following a PRBC transfusion.

RESULTS

A total of 347 infants were admitted between February 1, 2001 and March 31, 2002. Of these, 15 infants were excluded because no eosinophil counts were available, or because chromosomal anomalies were present ($n=6$). The remaining 332 infants had 1652 CBCs recorded that included eosinophil data. On average, infants across all age groups had an eosinophil count every 3.3 days, with no difference in the frequency of sampling between groups. This data set formed the basis of our observations, and demographic information for this population is provided in Table 1.

Overall, 19% of CBCs (313/1652) showed eosinophilia, with 51% of eosinophilic counts in the mild range (700 to 999 eosinophils/mm^3), 46% moderate (1000 to 2999 eosinophils/mm^3), and 3% in the severe range (≥ 3000 eosinophils/mm^3). Forty five percent of all infants had at least one instance of eosinophilia during their hospital stay and incidence decreased with maturity. There was no difference in the incidence of eosinophilia between AGA infants and those with PIH/SGA ($p>0.1$). For the remainder of the analysis, we consider these groups together.

The change in mean weekly eosinophil counts over time is shown in Figure 1. The four gestational age groups are shown separately. Eosinophil counts changed over time for the three preterm groups ($p<0.01$), but not for the ≥ 35-week infants. These more mature infants had higher eosinophil counts in the first week of life ($p<0.05$), and remained statistically unchanged over the first 4 weeks of life. This is in contrast to the increase in eosinophil counts with postnatal age seen in the more preterm infants in whom eosinophil counts peaked at week 4.

The prevalence and severity of eosinophilia varied by gestational age group, as is demonstrated by Figure 2. The panels show the individual eosinophil counts by day of life for the four gestational age groups. This figure illustrates the changing pattern of eosinophil counts with the most immature infants showing a protracted time course along with greater prevalence and severity of eosinophilia. In the first week of life, there were only four instances of eosinophilia in infants <27 weeks; three occurred proximal to PRBC transfusion, and one was associated with omphalitis. In contrast, for infants 27 to 29, 30 to 34, and ≥ 35 weeks gestation,

Table 1 Patient Demographics

Subjects (*N*)	<27 Weeks	27–29 Weeks	30–34 Weeks	≥35 Weeks
AGA (244)	$n=31$	$n=57$	$n=103$	$n=53$
SGA (88)	$n=7$	$n=19$	$n=39$	$n=23$
Gender (% male)	66	61	57	50
Race (%)				
Hispanic*	25	10	10	15
White	43	73	70	64
Black	22	3	9	8
Asian	14	8	10	10
Native American	9	7	1	3
Other	25	10	10	15
Mean GA±SD (weeks)				
AGA	25.4±1.0	28.5±0.8	32.6±1.4	37.4±1.9
SGA	25.6±1.0	28.8±0.7	32.7±1.4	37.7±1.8
Mean BW±SD (g)				
AGA	787±122	1213±228	1955±470	3034±691
SGA	692±154	984±278	1661±466	2758±1072
Delivery (% Cesarian)	46	63	57	46
Mean Apgar score±SD				
1 minute	3.0±1.2	5.0±1.9	6.0±1.7	6.0±2.1
5 minute	6.0±1.2	7.0±1.3	8.0±1.2	8.0±1.3

*Hispanic designation crosses all race groups.

there were 11, 15, and 19 respective instances of eosinophilia unrelated to infection or transfusion in the first week of life. Infants <30 weeks gestation exhibited a significantly larger percentage of infants with eosinophilia at some time during hospitalization than infants ≥30 weeks ($p<0.001$). Table 2 shows the incidence ($p<0.001$) and severity ($p<0.05$) of eosinophilia differed as a function of gestational age. Cases of eosinophilia were most frequent in the <27-week group, and least common in the ≥35-week group. Moreover, mild eosinophilia was most common in the ≥35-week group, and least common in the <27-week group. Most eosinophilia in the smaller infants was moderate to severe in nature.

Effects of infection and NEC on eosinophil counts were evaluated. In all, 61 infants had 174 eosinophil counts drawn in proximity to a documented infection, 59 of which showed eosinophilia (33.9%). A total of 113 infants had 178 counts drawn proximal to a suspected infection, and 16.3% of these counts showed eosinophilia. In all, 38% of <27-week infants, 45% of the 27 to 29-week infants, 21% of 30 to 34-week infants, and 29% of infants ≥35 weeks gestation had eosinophilia proximal to infection. Overall, only 26% of the eosinophilic counts in infants <30 weeks gestation were temporally associated with infection (sepsis or meningitis). NEC (pneumatosis intestinalis, free air with confirmatory pathologic findings) occurred in 14 infants spanning the gestational age range from 24 to 34 weeks (mean age of onset was 30.8±2.2 weeks corrected gestational age, 11 cases occurred in infants born at less than 30 weeks of gestation).[25] Six infants required surgical treatment, and eight were treated medically. The overall mortality was 50%, with 36% attributable to NEC. Eosinophilia proximal to the NEC occurred in 57% of the infants; three had mild, two moderate, and three had severe eosinophilia. Eosinophilia generally occurred within 24 hours of the diagnosis of NEC. A total of 57 eosinophil counts were obtained in these 14 infants, and 23 (40.4%) were eosinophilic. Of the infants with normal eosinophil counts, five of the six infants had acute, catastrophic NEC and died within 24 hours of onset, so no further eosinophil counts were obtained. Eosinophil counts from infants with documented infections and NEC are higher than those without ($p<0.0001$ and 0.01, respectively). We further analyzed these results by gestational age group (Figure 3), and showed these effects were more substantial in the immature infants.

The administration of PRBC to NICU patients was common, with the most immature infants receiving the greatest number of transfusions: 134 transfusions were given to 29 infants <27 weeks of gestation, 92 transfusions to 40 infants 27 to 29 weeks of gestation, 6 to 5 infants 30 to 34 weeks of gestation, and two transfusions were given to one infant >35 weeks of gestation. When eosinophil counts obtained within 7 days following a PRBC

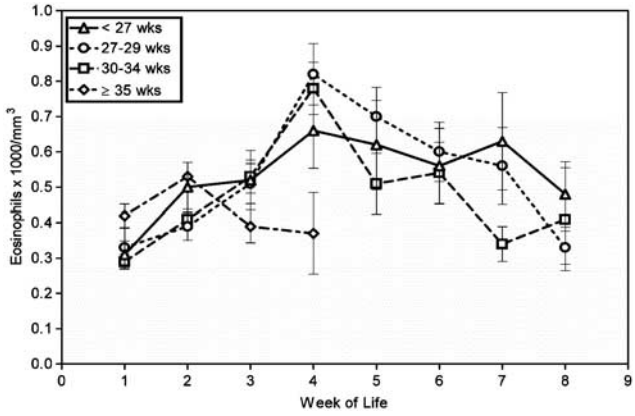

Figure 1. Average weekly eosinophil counts by gestational age. Mean eosinophil counts (±SEM) plotted against postnatal age (weeks) for infants born at different gestational ages (legend). A weekly average of eosinophil counts across all infants in each age group was calculated from the mean weekly count for each infant. The number of infants represented each week varied as follows: <27 weeks gestation: $n = 31$, 34, 25, 23, 24, 23, 19, and 23 for each successive week 1 to 8; 27 to 29 weeks gestation: $n = 59$, 53, 58, 49, 42, 37, 29, and 24; 30 to 34 weeks gestation $n = 120$, 95, 80, 37, 24, 19, 8, and 4; ≥35 weeks gestation: $n = 63$, 49, 15, and 4). Repeated measures analysis found significant differences in eosinophil counts over time for all infants except those ≥35 weeks gestation ($p < 0.05$). These infants had higher mean eosinophil counts on week 1 as compared to the other groups ($p < 0.05$). The table shows the number of infants included at each time point.

transfusion were compared to those from stable, uninfected infants, we found an increase in mean eosinophil count, as is demonstrated in Figure 4 ($p < 0.001$). In all, 37% of the eosinophilic counts in infants <27 weeks of gestation occurred proximal to a transfusion, with 33% of eosinophilic counts in infants 27 to 29 weeks of gestation occurring within this timeframe.

Of severe eosinophilia, 60% was temporally associated with documented infection, NEC, or PRBC transfusion. This association decreased to 50 and 30% for moderate and mild eosinophilia, respectively. In comparison, 37% of eosinophil counts in the normal range (0 to 700/μl) were temporally associated with these conditions.

Although 35% (41/116) of stable infants (never-infected or transfused) who regained birth weight prior to discharge (in positive nitrogen balance) exhibited eosinophilia, there was no correlation between the day of peak eosinophilia and the regaining of birth weight ($r^2 = 0.065$, $p > 0.10$).

Forty percent of infants in our study population received antibiotics during hospitalization for either suspected or documented infection. When sepsis was a concern, generally double or triple antibiotic coverage was used, making it impossible to draw any useful conclusions regarding the relationship between eosinophilia and individual antibiotics. All of these infants also had intravenous catheters for administration of antibiotics, so

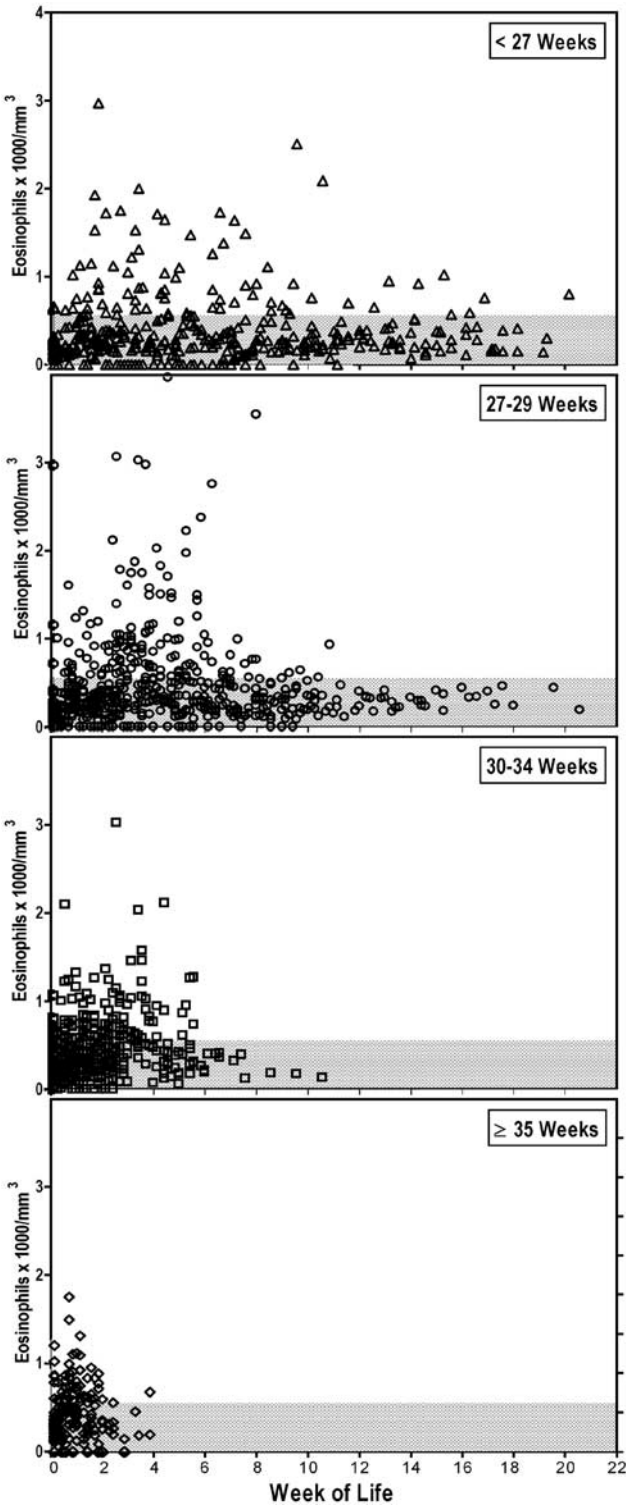

Figure 2. Distribution of eosinophil counts by gestational age and day of life. Scatter plots of all eosinophil counts from infants are separated by gestational age at birth (panels). Each point represents a single eosinophil count. The shaded regions delineate the normal eosinophil range. The *X*-axis shows postnatal age in weeks.

Table 2 Incidence and Severity of Eosinophilia across Gestational Age Groups

	All subjects	<27 Weeks	27–29 Weeks	30–34 Weeks	≥35 Weeks
Incidence of eosinophilia					
Eosinophilic patients (*N*)	148	28	49	46	25
(% of infants that age)**	(45%)	(74%)	(65%)	(32%)	(33%)
Number of CBC's/group	1652	459	541	475	177
Median #CBC's /baby (range)		12	7	3	2
		(1–25)	(1–21)	(1–13)	(1–7)
Mean counts/infants/day		0.3	0.3	0.3	0.4
Eosinophil counts ≥700	313	96	108	76	33
Severity of Eosinophilia†					
Mild 700–999 (#infants)		8	24	22	18
(% of infants that age)*		29%	49%	48%	72%
Moderate 1000–2999		18	23	22	7
(% of infants that age)		64%	47%	48%	28%
Severe ≥3000		2	2	2	0
(% of infants that age)*		7%	4%	4%	

*$p<0.05$ χ^2; **$p<0.001$.
†This portion of the table describes the risks of mild, moderate, or severe eosinophilia, among infants exhibiting eosinophilia throughout hospitalization, by counting only the largest eosinophil count for each case across age groups.

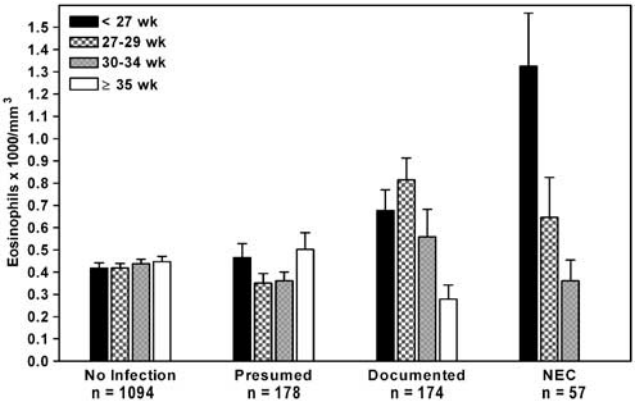

Figure 3. Effect of infection or NEC on eosinophil counts. Eosinophil counts (mean±SEM) for stable infants (no infection, no PRBC transfusion) are compared to those of infants with presumed or documented infection, and NEC separated by gestational age groups. The response to NEC is gestation related, with the most immature infants showing the most marked eosinophilia. The number of eosinophil counts in each category are shown.

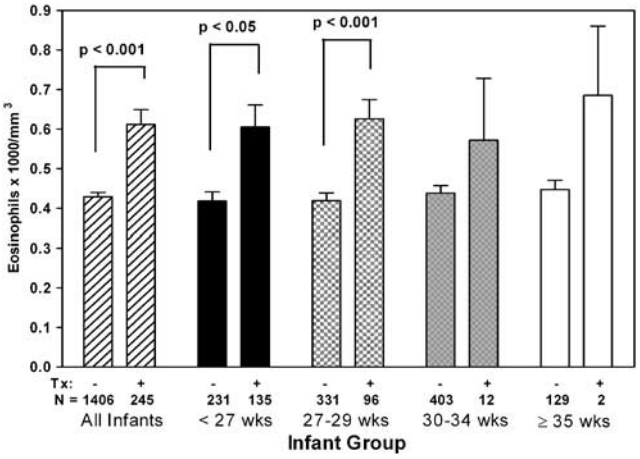

Figure 4. Effect of PRBC transfusion on eosinophil count in uninfected, stable infants. Eosinophil counts (mean±SEM) obtained from all stable infants (Tx−) were compared to those obtained proximal to PRBC transfusion (Tx+). Infants are separated by gestational age group as indicated, and the number of eosinophil counts in each group is shown. Note that the first pair of bars (striped) represents all age groups combined. Statistical comparisons (Mann–Whitney *U*-test) are indicated.

associations between eosinophilia and foreign bodies could not be independently explored. Although 98% of infants <27 weeks gestation underwent mechanical ventilation (mean duration 31 days), neither respiratory distress nor mechanical ventilation predicted eosinophilia. Two infants developed significant eosinophilia associated with milk protein intolerance.

DISCUSSION

This report improves the characterization of neonatal eosinophilia across a broad range of gestational ages. Although the precise effects of eosinophilia in preterm and term neonates are not known, it is known that eosinophils secrete granules that contain

several cytotoxic molecules: (1) eosinophil peroxidase (homologous to neutrophil myeloperoxidase), (2) major basic protein (toxic to helminths, protozoa and bacteria), (3) eosinophil cationic protein (with toxic ribonuclease activity), and (4) eosinophil-derived neurotoxin (EDN). EDN also has ribonuclease activity and may have a role in host defense against RNA viruses, such as the respiratory syncytial virus.[6] In addition, eosinophils release cytokines and chemokines that modulate inflammatory responses.[27] Proinflammatory factors include: IL-1, IL-6, IL-8, regulation upon activation normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein -1α (MIP-lα) and tumor necrosis factor-α (TNF-α). Eosinophils also contain lipid-derived proinflammatory substances (prostaglandin E2, thromboxane A2, leukotriene C4, 15-hydroxyeicosatetraenoic acid and lipoxin A 4) that are likely important in the allergic inflammatory reaction.[3] Immunoregulatory factors include IL-2, IL-4, IL-10, and interferon-γ.[27] Finally, eosinophils may also affect tissue remodeling and fibrosis by releasing transforming growth factors (TGF)-α[28,29] and TGF-β1.[5]

This ensemble of factors can work in concert to protect the host against infection, but can also produce tissue injury if their synthesis, release, and accumulation are not tightly regulated. Indeed, the accumulation of eosinophils and eosinophil proteins have been associated with the tissue injury in a number of diseases including asthma, ulcerative colitis, rheumatoid arthritis, psoriasis, and the encephalopathy seen in eosinophilia-myalgia syndrome.[30–32] Whether eosinophils contribute significantly to the pathology of neonatal disease states such as NEC is unknown; however, concern is warranted, based on extrapolation from what is known about adult disease states involving eosinophils.

In contrast to prior reports,[7,8,10,33,34] in our population, eosinophil counts varied as a function of both gestational age and postnatal age with the smallest infants (<30 weeks) exhibiting the highest incidence and a disproportionate severity of eosinophilia. Although this group of infants experienced more infections and more PRBC transfusions than their more mature peers, less than 60% of the eosinophilia seen in these smaller infants is explained by these factors. Factors that have previously been associated with eosinophilia, respiratory distress, and mechanical ventilation were prevalent in our most immature population, but the time course of these features differed from that of eosinophilia. Almost all of our smallest infants were intubated at birth for surfactant therapy, and the duration of mechanical ventilation (often for apnea of prematurity) averaged 1 month. We found eosinophilia to be less common in the early weeks of life in infants <30 weeks gestation, with high counts persisting into the second and third months of life.

One limitation of this retrospective study is that it is not possible to determine the individual contribution of uncontrolled factors such as infection, antibiotics, and the presence of foreign bodies such as IV's, central lines, and endotracheal tubes. All of these infants also had indwelling lines in place for administration of antibiotics, so the association of eosinophilia and foreign bodies could not be independently assessed. For that reason, these data do not disqualify the possibility that increased incidence of eosinophilia in more premature infants may reflect a physiologic and developmentally immature response to foreign antigen exposure.[10]

Overall, eosinophilia was most common in infants <27 weeks of gestation, and in those with documented infection, NEC, or PRBC transfusions, reinforcing the concept that infection or stress influence susceptibility to eosinophilia.[8] Differences in the time course of neonatal eosinophil counts suggest that developmental maturity is reflected by a higher initial eosinophil count that remains stable, while developmental immaturity is characterized by a lower initial eosinophil count that increases until 4 weeks of life, followed by a protracted decline to stabilization. Although the mechanism of the eosinophilia is unclear, the variability in eosinophil counts in the most preterm infants might reflect both an immaturity of granulopoietic regulation and antigen processing, as well as a corresponding vulnerability to infection and other stressors. This study improves our understanding of neonatal eosinophil counts by contrasting a broader range of gestational ages over a longer time period to establish the incidence and pattern of eosinophilia based on gestational age at birth, postnatal age, and identified clinical factors.

In contrast to the early neutrophil suppression associated with PIH, eosinophil counts were not affected by PIH when appropriately matched AGA infants were compared.[25] Similarly, intrauterine growth suppression did not affect the incidence of eosinophilia. These findings suggest that prematurity and ensuing postnatal events influence the regulation of eosinophils more than intrapartum conditions.

Although an association between eosinophilia and positive weight gain has been reported,[7] we found no correlation between the day of peak eosinophilia and the day on which birth weight was regained. One set of twin infants experienced eosinophilia that was possibly related to milk allergies, but other immune-mediated eosinophilias were not identified in our population. Similarly, there were no cases of hypereosinophilic syndrome, Loffler's syndrome, Omenn syndrome, Job's syndrome, or any drug-related eosinophilias identified in our population.[7–13]

In summary, we have shown that eosinophilia is common in the hospitalized neonate at all gestational ages. We found significant differences in patterns of incidence and severity based on gestational age, with the more immature infants experiencing increased incidence, and greater severity of eosinophilia. These data emphasize the impact of developmental immaturity on the eosinophil counts of hospitalized infants and raise concerns about the potential susceptibility of immature neonates to eosinophil-mediated tissue injury.

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