Blood eosinophil counts and arterial oxygen tension in acute asthma

Daniela Spallarossa, Oliviero Sacco, Donata Girosi, Giovanni A Rossi

Abstract

Objective—To investigate whether during acute asthma episodes a decrease in blood eosinophil count could correlate with the severity of the disease.

Design—Prospective study on paediatric asthmatic patients admitted for acute asthma exacerbation between January 1992 and August 1993. All patients were regularly followed up in an outpatient clinic and had had a complete clinical evaluation <1 month before admission.

Setting—Pulmonary division of the G Gaslini paediatric research institute, Genoa, Italy.

Subjects—21 asthmatic patients, 59 (SEM 9) months of age, admitted for acute asthma exacerbation. On the basis of clinical evaluation and the results of blood and microbiological tests performed during acute asthma exacerbations, patients were divided into two subgroups: infected (n=13) and non-infected (n=8).

Results—All but one of the patients showed a marked decrease in blood eosinophil count during the acute asthma episode, in comparison with recent count (<1 month before admission) obtained in clinically stable conditions: 662 (116) v 210 (54) eosinophils/mm³, p<0.0003. The decrease in the eosinophil count was more pronounced in the infected patients than in the non-infected patients, but the difference was not statistically significant (p>0.05).

Similarly, transcutaneous arterial oxygen pressure (Pao₂) values measured during acute asthma exacerbations tended to be lower in infected patients, without, however, reaching statistical significance: 8-6 (0-7) v 10-1 (0-9) kPa, p>0.05. The correlation between the decrease in blood eosinophil count and Pao₂ during the acute asthma exacerbations was significant in all the patients (r²=0-235, p=0-022) and in the non-infected patients (r²=0-653, p=0-015), but not in infected patients. In this latter subgroup, a significant negative correlation was found between blood neutrophil counts during acute asthma exacerbations and Pao₂ (r²=349, p=0-026).

Conclusions—During acute asthma exacerbations in atopic patients without clinical evidence of infection, the decrease in blood eosinophil count correlates significantly with the decrease in Pao₂, further supporting the role of eosinophils in allergic asthma.

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Keywords: acute asthma, blood eosinophils, arterial hypoxia.

Although the basic immunological defect in asthma is still unknown, continuing investigations are yielding insights into the pathogenic components of this disorder. Although bronchoalveolar lavage, bronchial biopsy, and in vitro studies have provided convincing evidence that mast cells, T lymphocytes, and eosinophils are important components of the inflammatory reaction in allergic as well as in non-allergic (intrinsic) asthma, only not only delineates the production of allergen specific IgE in the Airways, but also regulate the maturation, recruitment, and activation of eosinophils. Experimental exposure of atopic subjects with asthma to allergen inhalation results not only in degranulation of mast cells, but also in increased numbers of activated T lymphocytes and in recruitment of eosinophils. Similarly, in exercise induced asthma, degranulation of mast cells is associated in some patients with migration of eosinophils in the Airways. The role played by eosinophils in the pathogenesis of asthma has been debated for years. While these cells have been considered ‘beneficial components’ of the host reaction, able to suppress mediators of inflammation in immediate-type hypersensitivity reactions, there is increasing evidence that they have the potential to injure host tissue through the release of toxic oxygen radicals and cytotoxic proteins.

In this context, the presence of eosinophils in the bronchial mucosa and in the Airways has been found to be statistically correlated with damage to the Airways epithelium, including loss of epithelial junctions, and to bronchial hyperreactivity at baseline or after allergen challenge. Current concepts recognise that airway eosinophilia is the result of the efflux of circulating peripheral blood eosinophils, responding to chemoattractants that drive the cells toward the bronchial structures. These chemotactic stimuli have marked effects even on eosinophil activation, converting normal eosinophils into hypodense or degranulated eosinophils, and releasing mediators and cytotoxic products. Consistent with this hypothesis is the demonstration that, after allergen inhalation challenge, the increased eosinophilia observed in bronchial biopsies and in bronchoalveolar lavage is associated with the decrease of the numbers of circulating eosinophils. We therefore hypothesised that in ‘naturally occurring’ acute asthma episodes, a similar recruitment of eosinophils from blood.

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could also be demonstrated and that the decrease in circulating eosinophil numbers could correlate with the impairment of respiratory function.

Methods

PATIENT POPULATION
All the asthmatic patients admitted between January 1992 and August 1993 to the paediatric pneumology division of the Gaslini Institute because of acute bronchospasm severe enough to require hospital admission were retrospectively evaluated. The study inclusion criteria were: (1) a diagnosis of bronchial asthma, according to the definition of the American Thoracic Society; (2) the availability of former clinical records, including a venous white blood cell (WBC) total and differential count, performed within one month of the hospital admission while the patient was in a stable clinical condition; (3) no systemic or inhaled corticosteroids for at least 45 days before admission; (4) the availability of total and differential venous WBC counts and of transcutaneous arterial oxygen pressure (PaO$_2$) measurements, performed on hospital admission and before any systemic steroid treatment.

PATIENT EVALUATION
At hospital admission the diagnosis of an acute asthma exacerbation was based on the clinical signs of acute airway obstruction: dyspnoea with wheezing and prolonged expiration, tachypnoea with the use of accessory muscles of respiration, and tachycardia. Examination of the lungs showed wheezing and rhonchi and/or unequal breath sounds in all patients; latent wheeze was inducible in younger patients by the manual compression of the chest during expiration. On admission, routine blood tests and microbiological examinations on blood, serum, and nasopharyngeal secretions were performed in all patients by the central clinical laboratory of our institute. Eosinophil counts were performed with a Technicon H6000 (Technicon Instrument Corporation), a system that automatically counts and differentiates between leucocytes by an alkaline peroxidase method. Approximately 12,000 leucocytes were counted on each occasion. The coefficient of variation for the eosinophil counts was 7·5%. The total peripheral blood eosinophil counts at the hospital admission and the total peripheral blood eosinophil counts previously determined in the same patients under clinically stable conditions were used to estimate the blood eosinophil count decrease during acute asthma episode, so that the patients acted as their own controls. On the basis of the clinical evaluation and the results of blood and microbiological tests performed during acute asthma exacerbations, patients were divided into two subgroups: infected subjects and non-infected subjects. As an objective index of the severity of the asthma, non-invasive assessment of blood oxygenation was carried out at the bedside by transcutaneous oximetry (Tina D280, Radiometer) with a cutaneous probe at 42°C. The PaO$_2$ data were recorded for at least 1 h and the mean value was chosen. Patients were also classified as atopic or non-atopic according to the total and allergen specific serum IgE levels and skin reactivity to the most common environmental allergens in our area.

DATA ANALYSIS AND STATISTICAL EVALUATION
Data are expressed as arithmetic mean (SEM). Statistical analysis of the eosinophil counts was performed using the $t$ test. The relation between decrease in blood eosinophil count or neutrophil counts and PaO$_2$ values recorded by transcutaneous oximetry during acute asthma episode was assessed by the correlation test ($r^2$). Values less than 0·05 for $p$ were considered to be significant.

Results

PATIENT GROUP CHARACTERISTICS
Twenty one patients (11 males, 10 females, 59...
(SEM 9) months of age), all regularly followed by our outpatient clinic, fulfilled the inclusion criteria. One patient was evaluated during two subsequent asthma episodes. Sixteen patients (76%) were classified as sensitised to environmental allergens. Thirteen patients (62%) had clinical or laboratory signs of infection (infected patient group); eight patients (38%) had no signs of infection (non-infected group). All the patients without infection were sensitised to environmental allergens (table).

**EOSINOPHIL COUNT DECREASE DURING ACUTE ASThma EPSODES**

All patients but one showed a marked decrease in total blood eosinophil count during the acute asthma episodes, as compared with the previous counts under stable clinical conditions: 210 (54) v 662 (116) eosinophils/mm³ respectively, p<0.0003. The blood eosinophil count decrease was more pronounced in the 13 patients with clinical or laboratory signs of infection (713 (176) eosinophils/mm³ in stable conditions v 177 (69) during the acute asthma episode; p<0.003) than in the eight patients without signs of infection (573 (94) eosinophils/mm³ in stable condition v 268 (89) during the acute asthma episode; p<0.01). However, no statistically significant differences were observed between the infected and the non-infected groups in: (a) total blood eosinophil count determined in a stable period; (b) total eosinophil count measured during the acute asthma episode; and (c) the blood eosinophil count decrease (p>0.05, each comparison) (fig 1).

**PaO₂ VALUES DURING ACute ASThma EPSODES**

The non-invasive measurement of blood gases at the bedside by transcutaneous oximetry showed that the mean PaO₂ value during the acute asthma episodes was 9.2 (0.6) kPa when evaluating all the patients together. PaO₂ values tended to be lower in the infected group than in the non-infected group, at 8.6 (0.7) kPa and 10.1 (0.9) kPa, respectively but the differences were not significant (p=0.296) (fig 2). The arterial hypoxaemia was indeed related to the acute asthma episode, since all patients returned to normal PaO₂ values (>12.8 kPa) within two weeks after recovery.

**CORRELATION BETWEEN PaO₂ VALUES AND BLOOD EOSINOPHIL COUNTS**

Evaluating all the patients together or separately (infected and non-infected subgroups), no correlation was found between PaO₂ values and either the eosinophil counts during the acute asthma episodes or the eosinophil counts during the previous clinically stable period (both p>0.05, each comparison) (not shown). In contrast, a statistically significant correlation was found between PaO₂ values and the decrease in eosinophil count during the acute asthma episode in all patients (r²=0.235; p=0.022) (fig 3A), and in the non-infected group (r²=0.653; p=0.015) (fig 3B). In contrast, no significant correlation was found between PaO₂ values and the decrease in blood eosinophil count during the acute asthma episode in the infected group (r²=0.183; p=0.127) (fig 3C). Interestingly, in the infected group a statistically significant inverse correlation was found between the PaO₂ values and the total blood neutrophil numbers during the acute asthma episode (r²=0.350, p=0.026) (fig 4).

**Discussion**

In this study we have shown that in the vast majority of asthmatic children a naturally occurring acute exacerbation is associated with decrease in the blood eosinophil count, presumably because of pulmonary sequestration of eosinophils. We have also shown that the decrease in numbers of circulating eosinophils is strongly correlated with arterial hypoxaemia, recorded by transcutaneous oximetry. The correlation between decreased blood eosinophil counts and PaO₂ values was greater in atopic patients without clinical or laboratory signs of infection. In contrast, in patients with positive signs of infection, PaO₂ values correlated with blood neutrophilia measured during acute asthma exacerbations, rather than with the decrease in blood eosinophil count. Previous studies have suggested that eosinophils may be potent inducers of tissue...
proinflammatory substances, and cytotoxic
dependent mast cell activation,\(^7\)
products also have marked effects on cell
endothelial, bronchial epithelial, and
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Correlation between
eosinophil count
decrease and Pao2 values during asthma attacks in the
asthmatic lungs.\(^13\)\(^14\) The mechanisms by which
eosinophils are recruited into the lung struc-
tures in bronchial asthma are multiple and of
different origins.\(^5\)\(^7\)\(^10\) To accumulate in the air-
ways, peripheral blood eosinophils must
respond to chemotactic stimuli that drive the
cells within the bronchial and alveolar struc-
tures. Cytokines and mediators produced by
endothelial, bronchial epithelial, and immuno-
effector cells act as chemotactants for
eosinophils.\(^10\)\(^12\) In addition, most of these
products also have marked effects on cell
activation, converting normal eosinophils into
hypodense (or degranulated) eosinophils,
which release granule associated proteins,
proinflammatory substances, and cytotoxic
molecules.\(^10\)\(^14\) The best characterised
mechanisms for eosinophil recruitment are
chemotactic factors released after IgE
dependent mast cell activation,\(^7\)\(^8\) and after
allergen inhalation challenge increase numbers
of degranulated mast cells in the bronchial
mucosa have been described,\(^4\) associated with
increased proportions of eosinophils in
bronchial lavage\(^12\) and bronchial tissues.\(^4\)\(^11\)
Similarly, after specific allergen inhalation
challenge in atopic patients with asthma a
decrease in circulating eosinophil numbers has
been reported, correlated with the magnitude
of the late asthmatic response and with
changes in bronchial responsiveness.\(^18\) However, eosinophil infiltration
of the bronchial mucosa and degranulated
mast cells are also features common to
non-allergic, intrinsic asthma,\(^5\)\(^6\) and, as well as
mast cell derived mediators, it has been
demonstrated that even T cell derived cytokines can play
a major role in eosinophil biology.\(^22\)\(^23\) In this
case, in the airways of both allergic and
non-allergic asthmatic patients an intense
mononuclear cell infiltration is present,
including high proportions of activated T
lymphocytes.\(^5\)\(^24\) T cell derived cytokines
having effects on eosinophils include IL-3,
IL-5, and GM-CSF.\(^24\)\(^25\) IL-3, IL-5, and
GM-CSF may prolong the survival of
eosinophils in culture, may convert 'normal'
into 'hypodense' eosinophils and activate the
'resting' cells to release mediators or cytotoxic
products,\(^25\)\(^27\) and upregulate the expression
of adhesion molecules.\(^28\) IL-5 induces
eosinophilia in vivo,\(^29\)\(^30\) and in the guinea pig
model of allergic asthma the pretreatment
of the animal with anti-IL-5 antibody has been
shown to be effective in decreasing the
eosinophil efflux from the blood to the lungs.
In addition, IL-3, IL-5, and GM-CSF may
also upregulate the expression of adhesion
molecules involved in migration of cells such
as Mac-1 (CD11b/CD18 or CR3) on
eosinophils,\(^31\) and ICAM-1 on vascular
endothelial and airway epithelial cells.\(^32\) In
addition, eosinophils migrate in response to
factors that are also chemotactic for
neutrophils and include C5a, LTB4, hydro-
xeyeicosatic acids (HETEs), PAF-acether,
and formyl-methionine-leucine-phenylalanine
(f-MLP).\(^2\) In the present study we showed a
fall in circulating eosinophil numbers during
acute asthma episodes both in atopic patients
without clinical or laboratory signs of infection
and in patients with positive inflammatory
signs. Although the fate of eosinophils lost
from the circulation has not been determined,
the correlation with Pao2 values suggests that

![Figure 3](http://adc.bmj.com/) (A) Correlation between eosinophil count
decrease and Pao2 values during asthma attacks in all the
patients. (B) Correlation between eosinophil count decrease and Pao2 values
during asthma attacks in the non-infected patient group. (C) Correlation between eosinophil count
decrease and Pao2 values during asthma attacks in the infected patient group.

Figure 3 (A) Correlation between eosinophil count
decrease and Pao2 values during asthma attacks in all the
patients. (B) Correlation between eosinophil count decrease and Pao2 values during asthma attacks in the
non-infected patient group. (C) Correlation between eosinophil count decrease and Pao2 values during asthma attacks in the
infected patient group.

![Figure 4](http://adc.bmj.com/) Correlation between neutrophil counts and Pao2
values during asthma attacks in the infected patient group.
they may have been recruited to the lung, following the release of chemotactic factors by cells present in the airways. This hypothesis is in keeping with studies showing a fall in blood eosinophil counts\textsuperscript{19} and bronchoalveolar lavage eosinophilia\textsuperscript{6, 3}\textsuperscript{3} after allergen inhalation challenge. The causes of hypoxaemia in asthma are multiple, including bronchospasm, mucosal oedema, inflammatory changes of the airways, increased mucus secretion, and endoluminal mucus plug formation; the resulting decrease in alveolar Pa\textsubscript{o}{2} triggers vasoconstriction reflexes that often are responsible for ventilation/perfusion mismatching. In addition, because of the small diameter of the airways and the absence of collateral ventilation, atelectasis is frequent in young children during acute bronchospastic episodes.\textsuperscript{34} The eosinophils can play an important role in several of the mechanisms involved in the pathogenesis of bronchial asthma through the release of powerful mediators with spasmogenic, proinflammatory, and prosecretory effects.\textsuperscript{14, 35–38} The involvement of eosinophils in inducing morphological and functional changes in the airways in acute asthma is confirmed by the demonstration—provided by the present study—of a significant link between a fall in circulating eosinophil numbers and arterial hypoxaemia, particularly in atopics patients without clinical laboratory signs of infection. Interestingly, in patients with positive inflammatory signs, we found that Pa\textsubscript{o}{2} values correlated with blood neutrophilia rather than with blood eosinophil count decrease, suggesting that in different clinical settings other mechanisms, mediators, and cells might be involved in the functional damage to the respiratory system.

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